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OBSERVATIONS IN A CASE OF MUSCULAR DYSTROPHY, WITH REFERENCE TO DIAGNOSTIC SIGNIFICANCE

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DISEASES affecting the muscular system may present difficulties in diagnosis, particularly when they are characterized by atrophy of the muscles. For example, there are striking similarities in the course, signs and symptoms of the late dystrophy of distal type (Gowers) and of progressive muscular atrophy. The former belongs to the group of diseases which may best be described as the primary myopathies, or muscular dystrophies, and the latter to the so-called secondary myopathies.

In the primary muscular diseases, such as progressive muscular dystrophy, the pathologic process is thought to begin within the muscle fibers themselves; the changes result in weakness and paralysis in the presence of an apparently normal motor nerve. In the so-called secondary myopathies, the basic lesion lies within the spinal cord or the peripheral nerve, and the atrophy of the muscle is dependent on changes within the lower motor neuron.

It is possible that histologic examination might throw light on the course of the muscular dystrophies and, moreover, help to establish a diagnosis in some cases. The possibility of histologic differentiation of these two groups of diseases has been denied by Durante [1] (1902), but many authors do not accept this view. Among those who have described characteristic changes in dystrophic muscles are Pappenheimer,[2] Slauck [3] and Hassin.[4]

In this paper a further attempt is made to define the histologic differences between the primary and the secondary myopathies.

From the Nuffield Department of Orthopaedic Surgery (Miss Bowden) and the Department of Zoology and Comparative Anatomy (Mr. Gutmann), Oxford University.

1. Durante, G.: Anatomie pathologique de muscles, in Cornil, V., and Ranvier, L.: Manuel d'histologie pathologique, Paris, F. Alcan, 1902, vol. 2, p. 1.

2. Pappenheimer, A. M.: Beitr. z. path. Anat. u. z. allg. Path. **44**:430, 1908.

3. Slauck, A.: Pathologische Anatomie der Myopathien, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1932, vol. 16, p. 412.

4. Hassin, G. B.: J. Neuropath. & Exper. Neurol. **2**:315, 1943.

E.E.G.

METHOD

Two cases are described in which weakness was first noticed in the muscles of the lower extremities. Specimens of muscle were taken for biopsy and fixed immediately in a 5 per cent concentration of official solution of formaldehyde in isotonic solution of sodium chloride. Frozen sections were cut and stained with Gros's modification of the Bielschowsky method (for the determination of nerve fibers), hematoxylin and eosin and sudan III. Part of the specimen was embedded in paraffin, and the sections were stained with hematoxylin and eosin and with Mallory's phosphotungstic acid stain.

REPORT OF CASES

CASE 1.—*History.*—The patient was a man aged 42. On direct questioning, he admitted having noticed a slight loss of strength some time before October 1939. In November 1939, in the course of treatment for a simple fracture of the left ankle, drop foot was noticed by the physician. Electrotherapy improved the power of the weak muscles. During 1943 the hands became weak, and the patient had

Fig. 1.—Apathetic facial expression (myopathic facies).

difficulty in carrying weights and finally was unable to pull the trigger of a rifle with the right forefinger. In November 1943 there was sudden onset of pain in the left calf, related to exercise; subsequently, the pain became less severe. It was usually precipitated by walking but was not increased if he continued with exercise. There was no deterioration in power as the day went on. No dysphagia, diplopia or ptosis; no sphincter disturbance, and no loss of weight, dyspnea or anorexia was noted.

Past History.—The past history revealed nothing significant.

Family History.—There was no family history of a condition similar to the patient's. The patient had 2 normal boys, aged 11 and 13 years.

Examination.—Cranial Nerves: The facial expression (fig. 1) was apathetic, with weakness of orbital muscles and paralysis of the upper lip. Otherwise nothing abnormal was detected. The external ocular movements and the pupillary reactions were normal.

Spinal Nerves: There was generalized weakness of all muscle groups, including those of the trunk. The distal muscles were more affected than the proximal

ones, and the left leg was involved more than the right. There was bilateral paralysis of the latissimus dorsi and tibialis anterior muscles. Fasciculation was not visible.

Electrical Reactions: Tested with Bauwens'[5] machine, using stimuli of 1/1,000, 1/50 and 1 second duration, the threshold stimulus was measured in milliamperes. The muscles of the peroneal groups responded normally.

Muscle Tibialis Anterior	Duration, Sec.		
	1/1,000	1/50	1
Right	No response at 40 ma.	No response at 40 ma.	At 16 ma. sluggish contraction
Left	At 40 ma. small localized flicker	Nil	At 11.5 ma. sluggish contraction

Electromyographic Study: Both the right and the left tibialis anterior muscle showed only a few motor unit action potentials, some of which were polyphasic

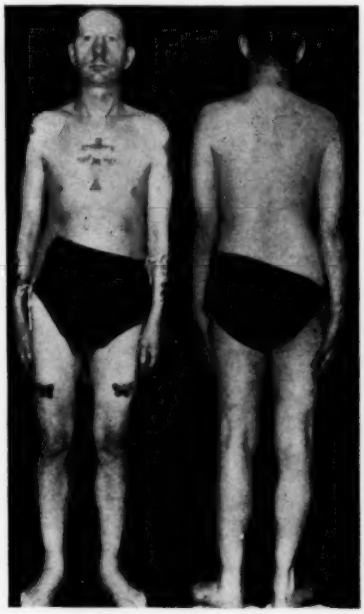

Fig. 2 (case 1).—Weakness of the abdominal muscles and absence of conspicuous localized wasting of the muscle groups.

and of low amplitude. In addition, action potentials which were indistinguishable from those of fibrillation were present in the right tibialis anterior muscle.

Reflexes: The reflexes were brisk in the upper limb. The abdominal reflexes were present. The knee jerks were brisk and equal on the two sides. The ankle jerks were absent. Plantar responses were of flexor type.

Sensation: There was no demonstrable sensory loss.

Clinical Diagnosis.—The clinical diagnosis was muscular dystrophy of late onset. The interesting features of the case were the late onset of disease, the absence of a family history of a similar disorder and the finding of action potentials resembling those of fibrillation. Records of isolated cases of progressive

5. Bauwens, P.: Brit. J. Phys. Med. **4**:150, 1941.

muscular dystrophy of late onset are not numerous in the literature, and the symptoms are varied; but cases similar to this one have been described (Nevin[6]).

Biopsy.—On Dec. 15, 1943 specimens of muscle from the left leg were taken for biopsy, with local anesthesia. The muscles were stimulated directly, using an induction coil and two needle electrodes. The peroneal muscles were rather pale but contracted briskly with a stimulus of 1.85 volts. The tibialis anterior and extensor digitorum longus muscles were exceedingly pale and fatty looking. With a stimulus of 5 volts a massive, sluggish and undulating response was obtained.

Progress (Oct. 20, 1944).—The patient complained of increasing generalized weakness; he found it difficult to run or hurry and his appetite was deteriorating, but there was no other change in the symptoms.

Weakness of the trunk muscles was more marked; the abdomen protruded, and there was postural kyphosis (fig. 2). There was no further paralysis, although generalized weakness was more noticeable. There was no obvious wasting of the small muscles of the hand (fig. 3).

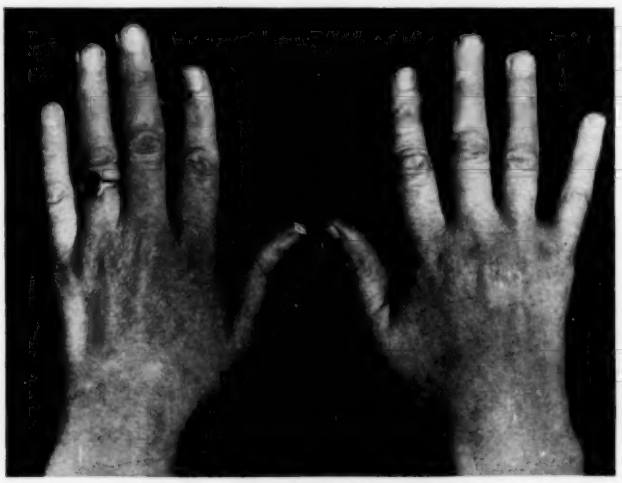

Fig. 3 (case 1).—Absence of wasting of the intrinsic muscles of the hand.

Electromyographic Study.—Right and Left Tibialis Anterior Muscles: The motor unit action potentials were polyphasic and of low amplitude. There was only doubtful fibrillation irritability on insertion of the concentric needle electrode, but there were some action potentials indistinguishable from those of fibrillation (fig. 4).

Right Latissimus Dorsi Muscle: Motor unit action potentials, of the same type as those seen in the tibialis anterior, were present. No fibrillation or fibrillation irritability was found.

Left Flexor Carpi Ulnaris Muscle: Motor unit action potentials were found, with some action potentials indistinguishable from those due to fibrillation irritability.

Histologic Observations.—Examination of the four biopsy specimens (taken on Dec. 15, 1943) showed varying degrees of atrophic change. The disease had apparently started at different times in the muscles, and thus an opportunity of observing the progress of the pathologic process was provided.

6. Nevin, S.: Quart. J. Med. **29**:51, 1936.

Atrophy was slight or absent in the peroneus longus and more advanced in the extensor digitorum longus muscle, and in the two specimens of the tibialis anterior muscle it was of extreme degree.

Peroneus Longus: There was a slight increase of fat and connective tissue between the muscle fibers. There was no indication of atrophy; the average diameter of the muscle fibers was 40 microns.

Cross striation was clearly visible, and there was no hyaline or fatty degeneration. There was apparently an increase in the muscle nuclei (fig. 5 *A*). The nuclei were arranged in rows and sometimes in clumps (fig. 5 *B*), an arrangement which is not found in normal muscle fibers. Often the nuclei were clustered in pairs, and this was especially conspicuous near the capillaries (fig. 5 *C*). No mitotic figures were seen, and there was no increase in the number of the nucleoli, such as can be found in early stages of denervation atrophy. The nuclei had one, and rarely two, nucleoli. Around many of the nuclei a halo of small granules was found (fig. 5 *D*). These were clearly visible in sections stained with silver but were not apparent in hematoxylin-eosin preparations. In normal muscle fibers granules are found regularly distributed at the level of the Q bands. Such granules were also observed in this muscle, but they were usually restricted to a narrow zone of the fiber close to the nucleus. This alteration in staining reactions and distribution of the granules is not explained, but it does suggest that some pathologic change may have taken place in the sarcoplasm of the muscle fibers.

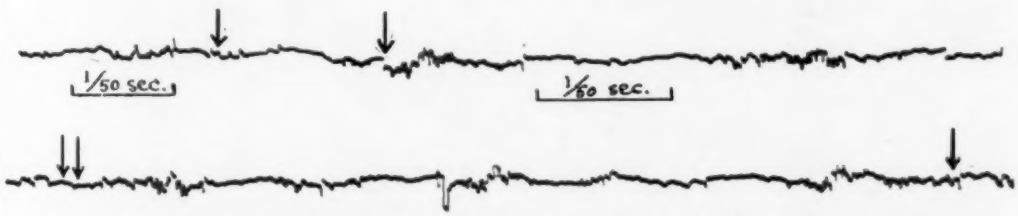

Fig. 4 (case 1).—Electromyographic tracings from the tibialis anterior muscle (during maximum voluntary effort), showing the bizarre, highly polyphasic motor unit action potentials and the spikes indistinguishable from action potentials characteristic of fibrillation, the latter being marked by arrows.

No empty nerve trunks were seen. The fibers were thick and myelinated. The pattern of innervation was normal. The terminal branches innervating the end plates lay near to the main trunks (fig. 5 *E*). No abnormality was found in the nuclei of the endplates.

Extensor Digitorum: There was a slight degree of atrophy, with some increase of fat and connective tissue between the muscle fibers. Many of the fibers were rather thick, some being even larger than normal (diameters of 90 microns were found), but there were also groups of rather thin muscle fibers. Some fibers were very large, appeared swollen and showed many spaces, with loosening of the compact arrangement of the fibrils. Cross striation was still clearly visible. There was an apparent numerical increase of the nuclei, for the muscle fibers appeared to be packed with them. Some of the nuclei were arranged in long rows, and in other parts there were large clumps of nuclei (fig. 5 *F*), often surrounded by fine granules. In silver preparations round or oval vacuoles were occasionally found between these clumps (fig. 5 *G*). They were represented by pale circles, surrounded with a halo of granules. Some of these vacuoles were about twice the size of the neighboring nuclei, but on an average they were of about equal size.

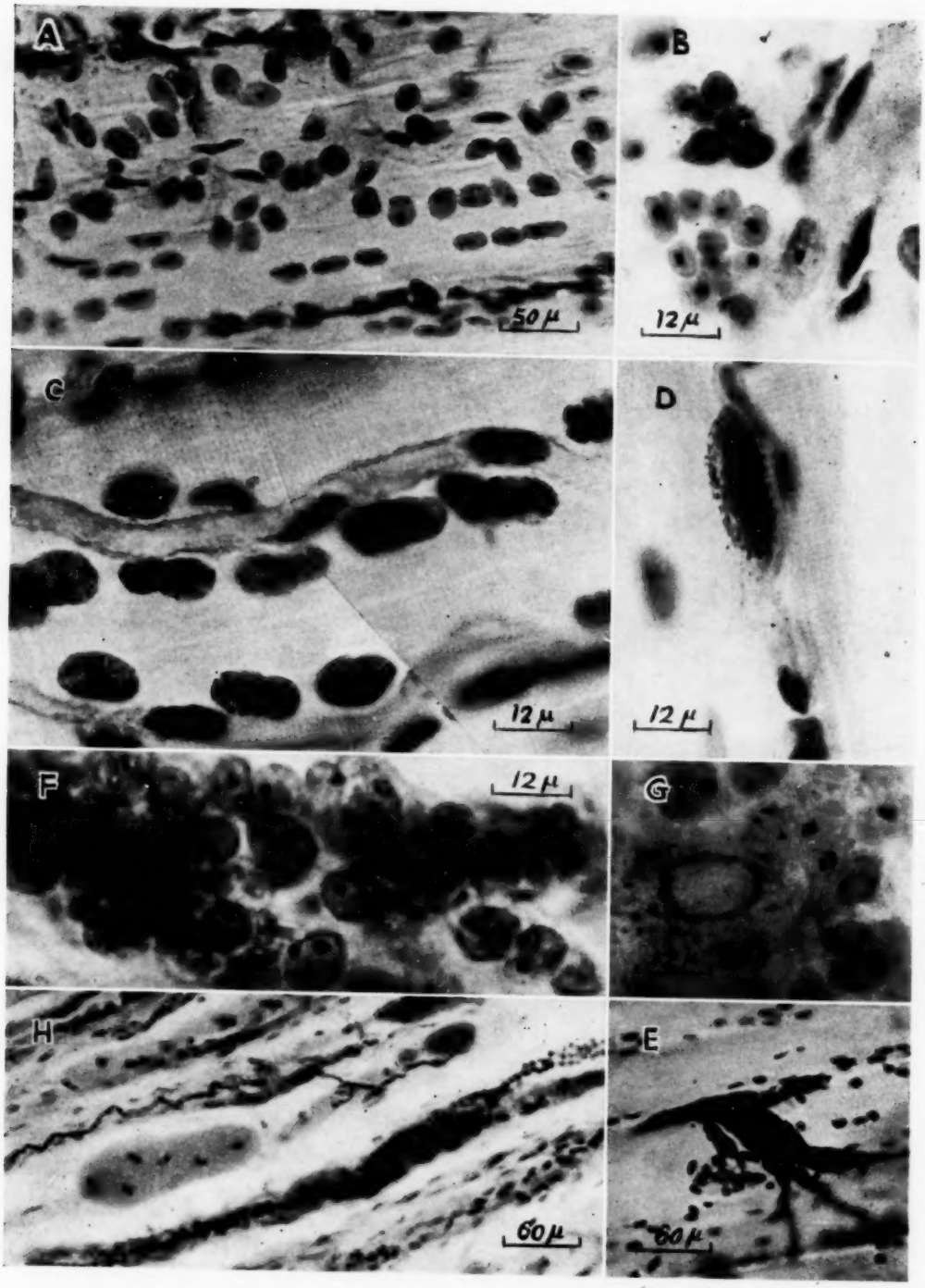

Figure 5

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Tibialis Anterior: The muscle showed an extreme degree of atrophy. A large part of it was replaced by connective tissue and fat. Scattered in the connective tissue were remnants of the muscle fibers, some thin and crowded with nuclei, others consisting of very large fragments filled with unstriated and apparently degenerated material (figs. 5 *H* and 6 *A*). However, it seemed that the muscle fibers had not all been attacked simultaneously, and some were still of fairly large diameter and the cross striation was intact. Some of these fibers showed a centrally placed row of nuclei arranged in long bands (fig. 6 *B*). Around these rows or clumps of nuclei there was often a clear halo, but the more peripheral part of the muscle fibers still showed cross striation (fig. 6 *C*). In some fibers fibrillary disruption was proceeding; in others there was only a peripheral mantle of striated fibrils around a clear central zone, and in others unstriated fibrils embedded in a granular material were just detectable (fig. 6 *D* and *E*). These changes possibly represent stages in the dedifferentiation of the protoplasm of the muscle fibers. Several muscle fibers were represented by tubes filled with pyknotic nuclei clustered tightly together (fig. 7 *B*); others contained in addition distinct eosinophilic masses, usually in the form of droplets (fig. 6 *F*). In such fibers hyaline degeneration seemed to be occurring. Many fibers, of varying size, were filled with irregularly distributed granules and groups of small nuclei. It was apparently in these fibers that fragmentation occurred (fig. 7 *A*). This fragmentation seemed to be the latest stage of the atrophy; intermediate stages could be found in which pieces of muscle fiber were still connected by fine strands. The same appearance is found in the late stages of denervation atrophy (Bowden and Gutmann [7]).

The nuclear changes were a striking feature of these dystrophic muscles. There might be an aggregation of nuclei, usually of uniform size. The majority were small and pyknotic and lay together in clusters; some showed signs of breakdown of chromatin. In others only the nuclear membrane stained darkly and irregularly (fig. 7 *C*), or a pale shadow might be all that was left (fig. 6 *E*). Around single nuclei or groups of nuclei clear halos often appeared (fig. 7 *D*). Two or three pyknotic nuclei might be surrounded by a clear zone; others were clustered in groups, or there were large, featureless pyknotic masses, probably formed by the coalescence of several nuclei. Finally, fragments of nuclear remains could be seen, and these were apparently undergoing ultimate dissolution.

Innervation.—There were no empty nerve trunks. In the larger trunks the nerve fibers were thickly myelinated, but in the individual Schwann tubes the

7. Bowden, R. E. M., and Gutmann, E.: Brain **67**:273, 1944.

EXPLANATION OF PLATE.

Fig. 5 (case 1).—*A* to *E*, musculus peroneus longus. *A*, muscle fibers crowded with nuclei, arranged in rows or clumps; *B*, muscle fiber with clumps of nuclei; *C*, nuclei arranged in pairs along the capillaries; *D*, muscle fiber with a halo of granules surrounding the nucleus; *E*, muscle fiber showing normal pattern of innervation.

F and *G*, musculus extensor digitorum, showing (*F*) many small nuclei arranged in clumps and (*G*) nuclei arranged in a cluster around a vacuole.

H, musculus tibialis anterior, showing extreme degree of atrophy of the muscle, with many thin muscle fibers crowded with nuclei and some large fragments of muscle fibers with no cross striation. The nerve fibers run for long distances between and along the muscle fibers.

In this figure, and in figures 6, 7 and 8, all sections are of muscle stained with the Bielschowsky method except where otherwise indicated.

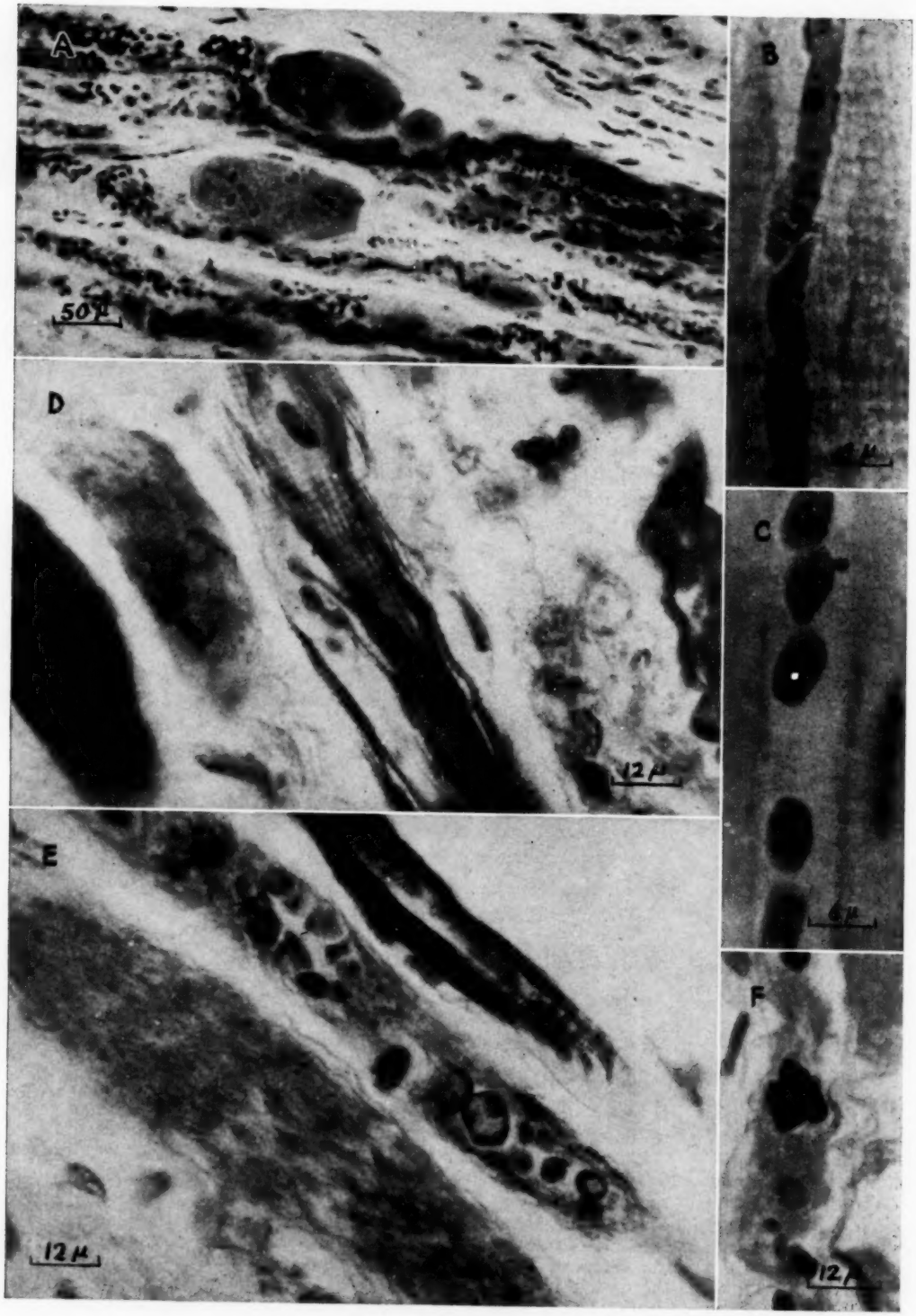

Figure 6

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diameter of some fibers was rather small in relation to that of the tube. The axon occasionally branched, and these branches ran along or across the muscle fiber or within the connective tissue, forming terminal knobs, such as are seen when regeneration of the axon has occurred (Gutmann and Young [8]) (fig. 8 *A*). Small rings (fig. 8 *B*) or large end bulbs (fig. 8 *C* and *D*) were seen on the surface of the muscle fibers or within the connective tissue. This pattern of innervation is not found in normal muscle but is typical of muscle reinnervated after some delay (Gutmann and Young [8]). The picture resembles abortive regeneration of nerve fibers.

Comment.—We may now attempt to reconstruct the sequence of changes in this case of progressive muscular dystrophy. The pathologic process is first indicated by the reaction of the nuclei and the granular constituents of the sarcoplasm. The muscle fibers appear crowded with nuclei, which are arranged in long rows or clumps. The reaction of the sarcoplasm is indicated by the appearance of granules, either in longitudinal zones or in a halo around some of the nuclei. At this stage there are no demonstrable degenerative changes in the nerve trunks or the nerve endings. In later stages there is a further increase of nuclear agglomerations; some of the nuclei become pyknotic, and later the chromatic material is dissolved. A striking feature, best seen in silver preparations, is the appearance of vacuoles between groups of nuclei. The process does not begin simultaneously in all muscle fibers. Muscle fibers with intact cross striation and large, bloated nuclei may be seen side by side with fragments of fibers represented by sarcolemmal tubes filled with clumps of pyknotic nuclei. The break-up of the muscle fibers appears to begin in the region of single or agglomerated nuclei, around which clear halos may be seen where the cross striated material has been destroyed. It may be that these spaces and the fragmentation of the fibers are caused by a lytic substance freed by the nuclei. Continuity of the muscle fibers is further lost by longitudinal splitting. Remnants of muscle fibers are found represented only

8. Gutmann, E., and Young, J. Z.: J. Anat. **78**:15, 1944.

EXPLANATION OF PLATE.

Fig. 6 (case 1).—Musculus tibialis anterior. *A*, extreme degree of atrophy of the muscle. Note large fragments of muscle tissue filled with unstriated material. *B*, muscle fiber in which the nuclei are arranged in a central row. *C*, muscle fiber with a central row of nuclei surrounded by a clear halo, only the peripheral mantle showing cross striated fibrils.

D, the different states of the muscle fibers. One muscle fiber is in process of fibrillary disruption; another shows a central halo with a peripheral mantle of striated fibrils. (Mallory's phosphotungstic acid hematoxylin stain.)

E, different states of the muscle fibers. One muscle fiber shows intact cross striations; another contains only a few fibrils and nuclei in the process of breakdown of the chromatin; another shows just a few unstriated fibrils embedded in granular material. (Mallory's phosphotungstic acid hematoxylin stain.)

F, muscle fiber containing a droplet of hyaline degenerated material between pyknotic nuclei. (Hematoxylin and eosin.)

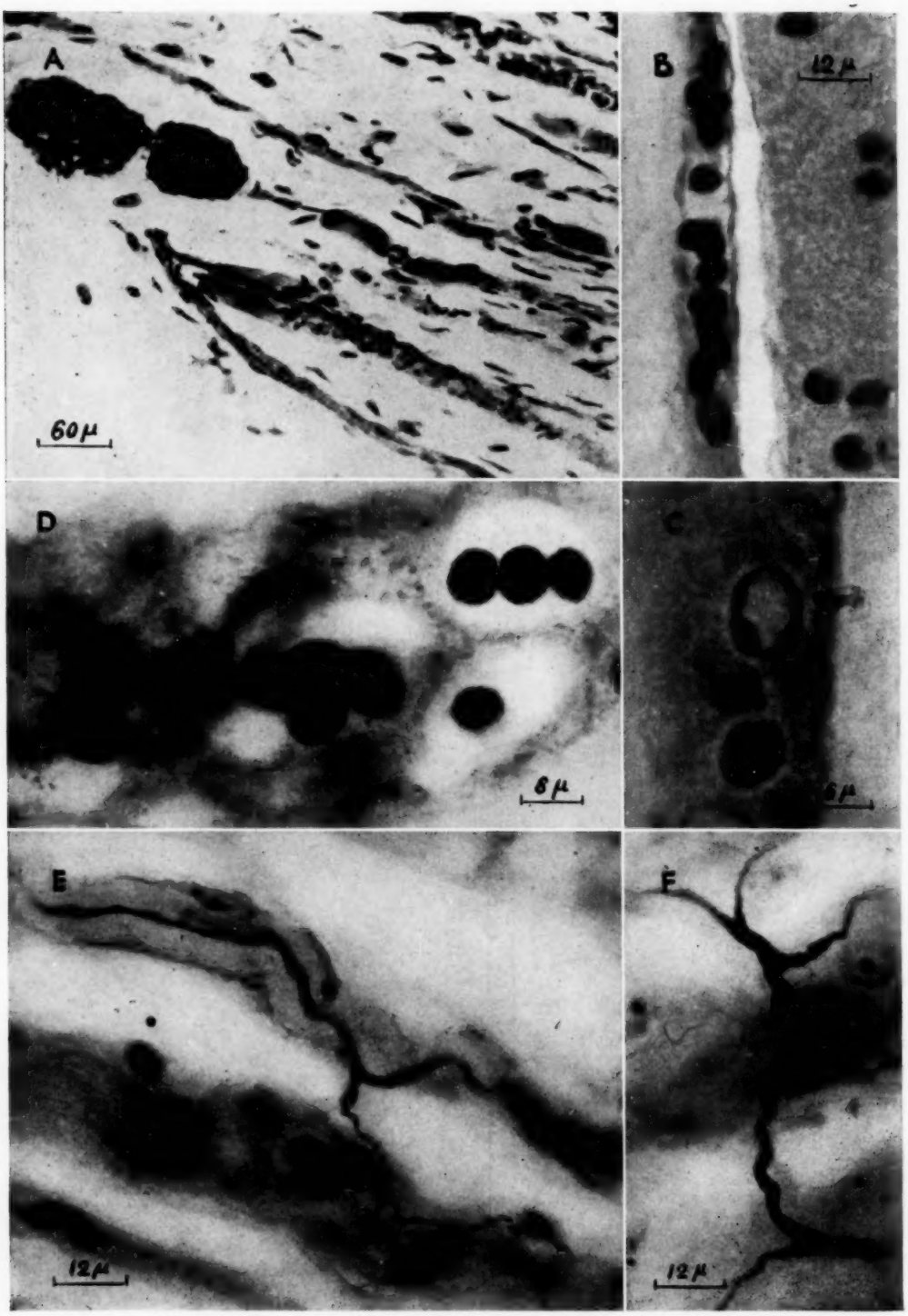

Figure 7

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by a thin band with a few nuclei and granules and with fibrils splitting up in all directions.

It is interesting to note that even in the latest stages cross striation of the thinnest muscle fibers may be intact, but it cannot be detected in fragments which are filled with irregularly distributed granules and disintegrating nuclei. In such fibers the cytoplasm apparently undergoes far reaching, and probably irreversible, changes, which appear to lead to loss of contact of the nerve with muscle fiber. If we may assume that the pathologic change leads to a disturbance at the myoneural junction and that the nerve fibers grow out again in an attempt to form new contacts, it is possible to explain the changes which present the picture of abortive regeneration of the nerve fibers.

There is no sign of degeneration in the larger nerve trunks, or of any previous degeneration, which would be indicated by an increase of the Schwann cells in these trunks. Moreover, the long "escaped fibers" running between the muscle fibers are often naked axons, which can be traced to a nerve fiber within a Schwann tube. Thus it is clear that in progressive muscular dystrophy the pathologic changes in the muscle fibers are primary and lead to a disturbance at the myoneural junction and to loss of contact of the nerve fibers. The terminal axons grow out farther in an attempt to form new contacts, but the changes in the muscle fibers are usually too far advanced to allow successful reinnervation.

Since there are obvious differences between the so-called primary and secondary myopathies, histologic examination of the muscle is likely to be of value both in diagnosis and in classification.

In a comparison of the primary and the secondary myopathies, two questions have to be considered: 1. Where do the pathologic changes in progressive muscular dystrophy begin, and what is the sequence of events? 2. Are the histopathologic changes in the dystrophies specific and therefore distinguishable from those of the secondary myopathies?

1. Histologic Observations: Histologic studies suggest that the first reaction to an unknown pathologic agent is one of the nuclei and the granular constituents of the sarcoplasm. The nuclei react with an apparent numerical increase; and they form rows and clumps, which are not found in normal muscles. There is no increase in the number

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EXPLANATION OF PLATE.

Fig. 7 (case 1).—Musculus tibialis anterior. *A*, extreme degree of atrophy. A muscle fiber filled with irregularly distributed granules is seen in the process of fragmentation. *B*, muscle fiber filled with clumps of pyknotic nuclei. (Hematoxylin and eosin.) *C*, part of a muscle fiber with one nucleus showing breakdown of the chromatin. *D*, groups of nuclei surrounded by clear halos. *E*, single Schwann tube containing a nerve fiber which branches off and runs along a muscle fiber. *F*, nerve fiber running across the muscle fiber.

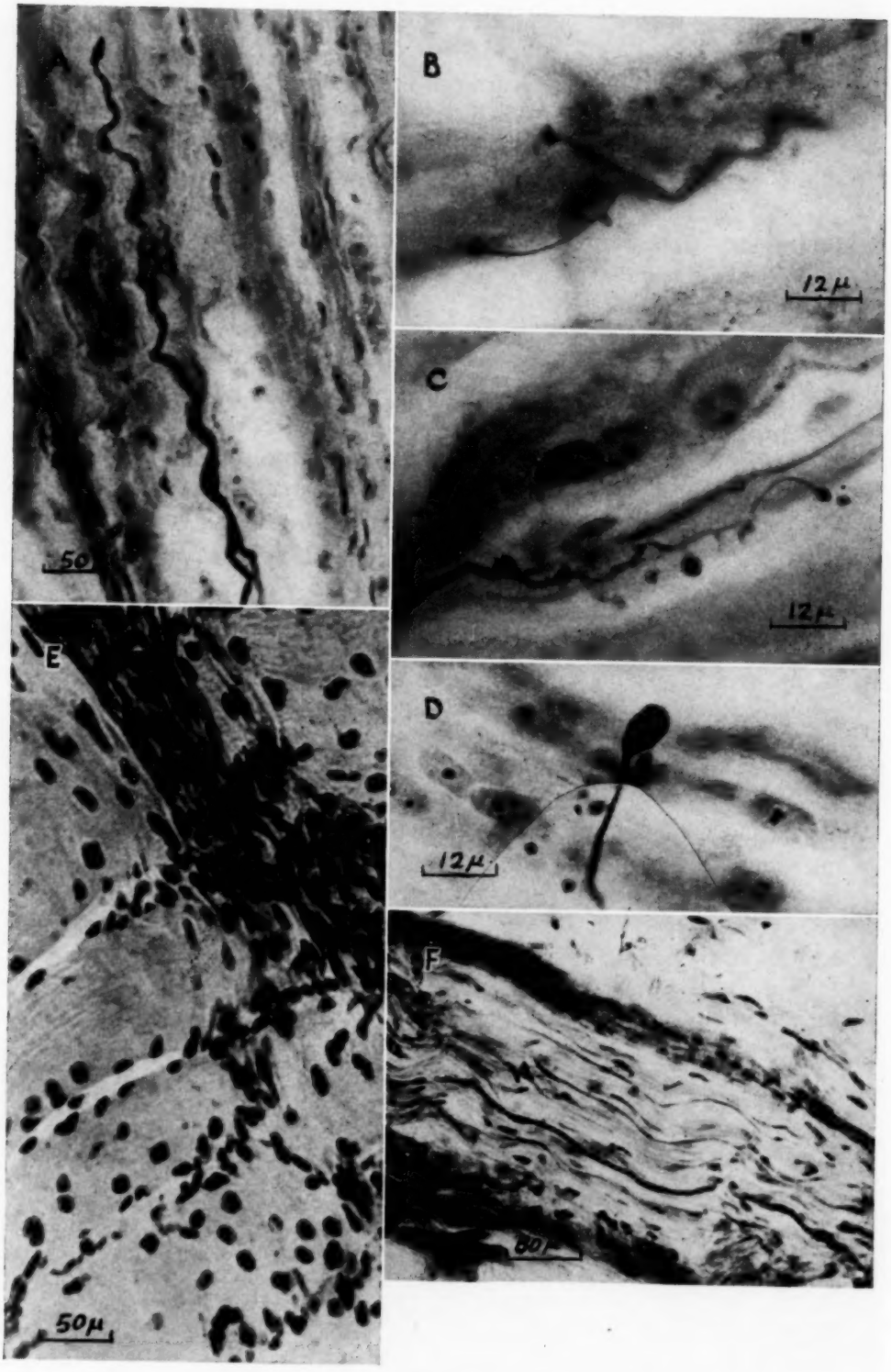

Figure 8

(See legend on opposite page)

of nucleoli, such as is found in denervations. In these early stages of the disease the muscle and nerve fibers show no pathologic changes. There is no indication that the process starts in the interstitial tissues, as suggested by Babes and Marinesco.[9] In the early stages the nuclear reaction is conspicuous, but there is no inflammatory reaction or increase in the connective tissue. Erb [10] described hypertrophic muscle fibers as typical of the early stages of the disease. These observations led him to the conclusion that the disease begins with hypertrophy of the muscle fibers, which is followed by atrophic changes. No definite confirmation of this assumption was found in the present case, though it was not one of pseudohypertrophic muscular dystrophy. In the later stages the nuclei undergo changes leading to their dissolution, and this process is accompanied by fragmentation and ultimate replacement of the muscle fibers with connective tissue. The onset and course of the process vary in the different muscle fibers. Thus, thin muscle fibers with intact cross striation and nuclei may be found side by side with large fragments of muscle filled with irregularly distributed granules and clumps of nuclei. Pyknosis and clustering of the nuclei, dissolution of the chromatin and formation of vacuoles are stages which seem to be significant.

The agglomeration of the nuclei in rows or clumps has been described by most authors. Lewin [11] described the "proliferating nuclei" as "myophages" and referred to their "phagocytic function." He stated that these myophages invade and destroy the contractile substance, forming lacunas or irregular spaces, which may contain fragments of striated material. This material could also be seen within the myophages themselves. Lewin, and afterward Pick,[12] identified the "myophages" with Köllikers osteoclasts.

It is, however, necessary to distinguish the halos and lacunas which are formed around single pyknotic nuclei, or around clumps of them, from the vacuoles appearing between the nuclear masses. There is

9. Babes and Marinesco, cited by von Meyenburg.[15]
10. Erb, W.: Deutsche Ztschr. f. Nervenh. **1**:173, 1881.
11. Lewin, A.: Deutsche Ztschr. f. Nervenh. **2**:139, 1892.
12. Pick, F.: Deutsche Ztschr. f. Nervenh. **17**:1, 1900.

EXPLANATION OF PLATE.

Fig. 8 (case 1).—*A* to *D*, musculus tibialis anterior. *A*, nerve fiber running for a long distance between the muscle fibers and within the connective tissue. Note the terminal knob. *B*, nerve fiber ending on a muscle fiber, with knobs and end rings. *C*, nerve fibers running along a capillary and ending in knobs. *D*, nerve fiber ending on a muscle fiber with a thick end knob, characteristic of a regenerated nerve fiber.

E and *F* (case 2), musculus peroneus longus, showing (*E*) a denervated muscle with empty Schwann tubes and end plates, and (*F*) nerve trunks containing a few thin, apparently regenerated nerve fibers.

no indication that the nuclei invade the muscle fibers, but halos or lacunas undoubtedly appear around them. Here the cross striated fibrils are destroyed, possibly by a lytic agent from the pyknotic and fragmenting nuclei. This is a very late stage, which ultimately leads to fragmentation of the muscle fibers. At an earlier stage small vacuoles appear between masses of the nuclei, and it is possible that they are a product of hyaline degeneration.

It is interesting to note that even with advanced changes cross striation of the thinnest muscle fibers may be intact, but it cannot be detected in fragments which are filled with irregularly distributed granules and disintegrating nuclei. In such fibers the constitution of the cytoplasm apparently undergoes far reaching, and probably irreversible, changes, which lead to loss of contact of the nerve with muscle fibers.

Few authors seem to have studied the nerve fibers in dystrophic muscles. Pappenheimer [2] found no changes in the intramuscular nerve fibers. This is true in the early stages, but in later stages the progressive changes in the muscle fibers lead apparently to a disturbance at the point of contact. Although the axons grow out in an attempt to form new contacts, in view of the advanced changes in the muscle fibers, this attempt may not always be successful.

The finding of action potentials characteristic of fibrillation is significant (fig. 4). Such an observation has not been recorded previously in cases of muscular dystrophy. However, the histologic changes offer a possible explanation. The pathologic alterations do not occur simultaneously in the different muscle fibers, and therefore detection of the action potentials of characteristic fibrillation may be difficult.

Polyphasic motor unit action potentials are occasionally observed in normal muscles, but they occur most frequently during reinnervation (Weddell, Feinstein and Pattle [13] and Bowden [14]). Their presence may represent the successful reinnervation of some muscle fibers. The action potentials in the tibialis anterior (fig. 4) were of low amplitude, and it is noteworthy that they were of bizarre shape and that, although they were polyphasic they were not exactly similar to those found during reinnervation. These action potentials may represent the electrical activity of grossly abnormal muscle fibers. Another possibility is that this activity originates in fibers which are abnormally scattered in space, and a third is that, owing to the disease process, the fibers of the single motor unit are not acting synchronously. Histologic observations lend

13. Weddell, G.; Feinstein, B., and Pattle, R. E.: Lancet **1**:236, 1943; Brain **67**:221, 1944.

14. Bowden, R. E. M.: Unpublished material.

support to the first suggestion but do not exclude the others. Further observations on this point are necessary.

We may conclude that progressive muscular dystrophy is a primary myopathy, as suggested by Durante, Friedreich and Lichtheim. Some authors have described changes in the spinal cord, and this observation would point to a central origin. But these lesions were on the whole not considered commensurate with the intensity and the extent of the changes in the muscles (Hassin [4]). Moreover, most of the authors have found no pathologic change in the nerve cells (von Meyenburg [15]).

2. Histologic Differentiation of Primary and Secondary Myopathies: That there are changes typical of dystrophic muscles has been stated by some authors. The observations reported in this paper were made in only 1 case of muscular dystrophy; however, the features were so striking that a distinction between the two types of disease could be made easily. Study of more material is, of course, necessary. Kure and associates [16] claimed to have produced dystrophic changes experimentally in muscle after severance of the sympathetic nerve trunk. The essential changes which they thought characteristic of progressive muscular dystrophy were as follows: great differences in size of muscle fibers, appearance of some hypertrophied fibers, increase of interstitial tissue, appearance of rounded muscle fibers and formation of vacuoles in the muscle fibers. None of these changes can be considered specific (in 1 case these changes were described by Kure and his associates only seven days after sympathectomy), and there is neither any evidence of the mechanism which they suggested nor any possibility of distinguishing progressive muscular dystrophy by these criteria.

Slauck [3] contrasted the arrangement of the muscle fibers in the two conditions; the fibers are irregularly distributed without grouping into bundles in cases of dystrophy, while in cases of denervation atrophy they are grouped in bundles. He also described the destruction of the muscle fibers by the "endogenous," more centrally placed, nuclei in cases of dystrophy and contrasted this with the destruction of the fibers by subsarcolemmal nuclei in cases of denervation atrophy (Slauck [3]). However, he did not state what stages of denervation were observed and compared. Comparison of dystrophic muscle with muscle in the late stages of denervation atrophy does not allow such a clearcut distinction.

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15. von Meyenburg, H.: Die quergestreifte Musculatur, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 9, pt. 1.

16. Kure, K.; Hatamo, S.; Shinosaki, T., and Nagano, T.: Ztschr. f. d. ges. exper. Med. **47**:89, 1925.

Homogenization, myofibrillary disruption, myophagia and fatty metamorphosis, with the ultimate formation of a connective tissue scar, have been considered primary degenerative changes independent of the condition of the spinal cord (Hassin[4]). However, in the late stages of denervation atrophy (twenty years of denervation or more) the changes in the muscle are similar to those observed in the late stages of dystrophy. Swelling, pyknosis and dissolution of the nuclei; formation of rows, and spherical agglomerations are all noted, in addition to longitudinal splitting, myofibrillary disruption and fragmentation of the muscle fibers. Hyaline and vacuolar degeneration of the muscle fibers and extreme increase of fat and connective tissue can be found with both disorders. In fact, the picture in the advanced stages of denervation atrophy is essentially the same as that of the muscle fibers in case 1. In denervated muscle the changes leading to fragmentation of the muscle fibers, associated with nuclear dissolution, are seen only in the very latest stages, while they apparently develop much more rapidly in dystrophic muscles. In both the process within the muscle fiber ultimately leads to cell death.

Thus, we may conclude from the material at our disposal that no clear differentiation between primary and secondary myopathies is possible when the state of the muscle fibers is considered alone. However, a distinction can be made when the innervation is observed. In cases of muscular dystrophy the changes in the muscle fibers are found while innervation is still intact or a pattern of terminal abortive regeneration is present. In cases of atrophy of neural origin denervation is indicated by the empty nerve trunks. This fact is demonstrated by the following case.

Case 2.—*History.*—A boy aged 15 years had gradual onset of pain in the ankles, weakness and clawing of the toes at the age of 13½ years.

Past and Family Histories.—The histories revealed nothing of significance.

Examinations (Oct. 9, 1942).—The patient appeared pale and unhealthy; he was of the asthenic type. There was a high stepping gait. There were mild kyphoscoliosis of the lower dorsal region and extreme talipes cavovarus of both feet, with clawing of all toes.

Cranial Nerves: There were slight paresis of the right external rectus muscle and an apathetic facial expression. Otherwise, nothing abnormal was detected.

Spinal Nerves: There was no localized thickening of the nerve trunks. The intrinsic muscles of the hands showed slight wasting. The abdominal reflexes were present and brisk. In the lower limbs, there were weakness and wasting of the right and left quadriceps muscles (which acted only against gravity) and slight weakness of the hamstrings and the medial popliteal group of muscles. Of the lateral popliteal muscles, there was feeble action of the extensor digitorum longus on both sides. The right tibialis anterior was barely active; the other muscles were paralyzed. Knee and ankle jerks were absent. The plantar responses were of flexor type.

Electrical Reactions: Reaction of degeneration was present in the paralyzed muscles, with feeble faradic responses in the paretic muscles.

Sensory Tests: No changes in sensation were noted.

Laboratory Studies: The Wassermann reaction of the blood was negative. Spinal puncture revealed an initial pressure of 100 mm., with no block. The fluid

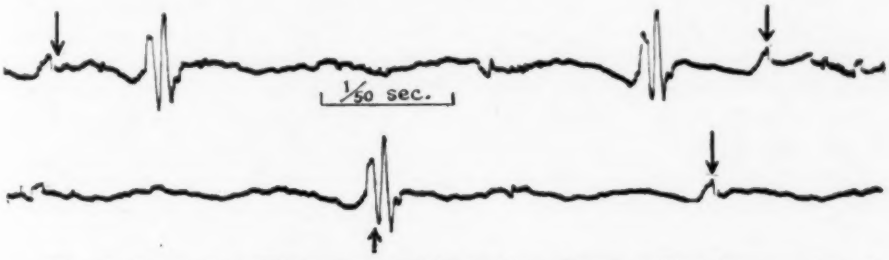

Fig. 9 (case 2).—Electromyographic tracing (same calibration as that in figure 4) from the first dorsal interosseus muscle of the right hand during maximum voluntary effort. Three normal motor unit action potentials (upward pointing arrows) and action potentials characteristic of fibrillation (downward pointing arrows) are shown.

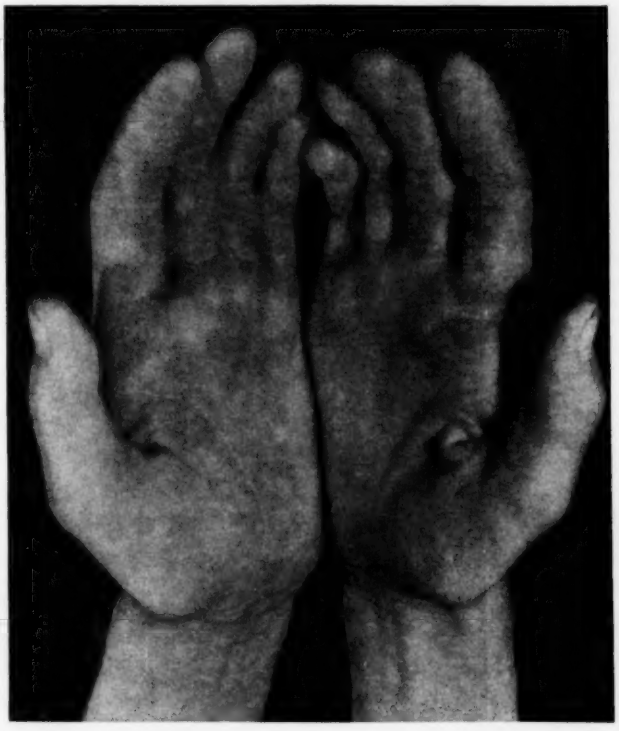

Fig. 10 (case 2).—Atrophy of the intrinsic muscles of the right hand, with clawing of the digitis.

was clear and did not clot. The protein measured 200 mg. and the chlorides 700 mg., per hundred cubic centimeters. The cell count revealed 2 lymphocytes and 1 red cell, per cubic millimeter.

Sweating Test (Dr. Ludwig Guttmann): There was symmetric hyperhidrosis below the knees.

Roentgenographic Study: A roentgenogram of the spine revealed no evidence of spina bifida and no osteochondritis.

Biopsy of Fibular Communicating Nerve (sensory) (W. Holmes).—"The specimen showed no noteworthy abnormalities. There was no degeneration of the axons or of the myelin or hyperplasia of the sheaths and no inflammatory reaction. There was no evidence of neuritis, and the central neurons must have been undamaged, as the axons were intact."

Electromyographic Study.—The first dorsal interosseus muscle of the hand showed both motor unit action potentials and potentials characteristic of fibrillation (fig. 9).

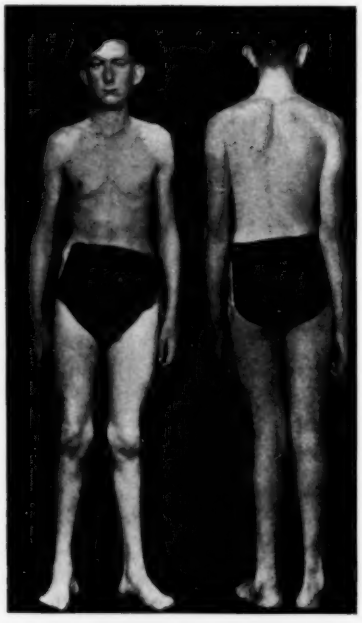

Fig. 11 (case 2).—Dorsal kyphoscoliosis, genu valgum and clawing of the feet, with varus deformity of the heels. Note the conspicuous wasting of the muscles of the right hand and the distal part of the lower limbs.

Progress.—There were increasing ataxia and weakness, necessitating bilateral arthrodesis of the tarsus (May 19, 1943), and progressive atrophy and weakness of the intrinsic muscles of the hand (figs. 10 and 11, taken on Oct. 3, 1944).

Diagnosis.—The diagnosis was peroneal muscular atrophy.

Histologic Observations.—Examination of the peroneus longus showed little atrophic change in the muscle fibers but some increase in connective tissue and fat. There were no nuclear changes resembling those found in case 1, but denervation of some muscle fibers was indicated by an increase in the number of nucleoli. In the subsarcolemmal nuclei, two to four nucleoli were found, as compared with the one or two nuclei seen in normal muscle.

The degree of innervation varied in different nerve trunks. A few trunks contained thick, apparently normal fibers. Many empty nerve trunks and empty end plates were found (fig. 8*E*). However, occasionally a nerve trunk contained a few rather thin nerve fibers, indicating early reinnervation of a denervated trunk (fig. 8*F*).

Almost complete denervation had taken place, but the small degree of atrophy indicated that the time of denervation had been short.

The histologic changes show a lesion of the lower motor neuron, but of course do not indicate where this lesion is situated, for the picture in the muscle will be identical whether the cord or the peripheral nerve is affected. However, the level of the lesion can usually be decided by clinical examination. In this case the normal sensation and the normal appearance of the sensory nerve pointed to predominant involvement of the motor nerve cells. It is interesting that there were a few normal nerve trunks and that there were a few containing regenerating fibers. Some anterior horn cells must have been spared, while in others the changes may have been reversible to some extent, thus enabling the cells to send out new axons.

SUMMARY

A case of progressive muscular dystrophy is described.

The early changes consist in a reaction of the nuclei and the granular constituents of the sarcoplasm. In later stages there is complete dedifferentiation of the striated material, leading to fragmentation of the muscle fibers, accompanied by a breakdown of the chromatin of the nuclei.

The late changes in dystrophic muscle fibers are identical with those observed in the final stages of denervation atrophy.

In the case of progressive muscular dystrophy the nerve fibers in the nerve trunks remained intact; but degeneration of the muscle fibers apparently led to loss of contact at the myoneural junction, and this was followed by abortive regeneration of the terminal nerve fibers.

Thus, the appearance of advanced atrophy in the muscle fibers, intact large intramuscular nerve trunks and abortive terminal regeneration of the nerve fibers were characteristic features of muscles in a case of progressive muscular dystrophy.

In cases of the so-called secondary myopathies, such as peroneal muscular atrophy, the nerve trunks are empty or contain both normal fibers and empty Schwann tubes. They may, however, occasionally contain regenerated nerve fibers. This may indicate that some of the anterior horn cells have not undergone irreversible changes but are capable of sending out new axons.

Biopsy of muscle with study of the pattern of innervation may afford valuable aid to diagnosis in unusual cases of muscular atrophy and weakness.

Prof. H. J. Seddon gave us permission to publish these cases.

Wingfield-Morris Orthopaedic Hospital.

EFFECTS OF *l*(+)GLUTAMIC ACID AND OTHER AGENTS ON EXPERIMENTAL SEIZURES

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CLINICAL reports [1] of the efficacy of glutamic acid in the symptomatic therapy of patients with petit mal and psychomotor epilepsy prompted the following investigation of the effects of this amino acid on electrically and chemically produced convulsions in laboratory animals, in order to determine whether glutamic acid could be shown experimentally to be an anticonvulsant agent and to compare its efficacy and mechanism of action with other anticonvulsant drugs.

METHODS AND PROCEDURES

Mice, rats, cats, rabbits and monkeys were used in metrazol [2] experiments. Rats, cats, rabbits and monkeys were employed for a variety of electric shock experiments. The effect of glutamic acid was also investigated in rats in which the electric shock threshold had been previously lowered by hydration (produced by orally administered water or by experimental selective loss of extracellular electrolyte). Electric shock seizures were induced by an Offner 60 cycle alternating current apparatus. Spiegel corneal electrodes were employed. For direct cortical stimulation (rabbits) single condenser discharges were delivered through epidural electrodes. Electroencephalograms were recorded with a Rahm encephalograph; standard scalp electrodes were used with monkeys and epidural leads with rabbits.

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Financial assistance was received from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association; the Research Fund, University of Utah School of Medicine, and the Abbott Laboratories.

1. (*a*) Price, J. C.; Waelsch, H., and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures, J. A. M. A. **122**:1153-1156 (Aug. 21) 1943. (*b*) Waelsch, H., and Price, J. C.: Biochemical Aspects of Glutamic Acid Therapy for Epilepsy, Arch. Neurol. & Psychiat. **51**: 393-396 (April) 1944.

2. Supplied by the Bilhuber-Knoll Corporation.

The natural *l* (+) isomer [3] of glutamic acid, rather than the racemic form, was employed in these experiments, inasmuch as Waelsch and Price [1b] suggested that the therapeutic effects could be ascribed to the former compound. It was given orally either in an acacia suspension or as a solution of the sodium salt. The latter was also employed for parenteral administration. The sodium salt was prepared by neutralization with sodium hydroxide to p_H 7.0. Doses employed ranged from 0.25 to 6.0 Gm. per kilogram of body weight calculated as the amino acid and were designed to cover and exceed, on a body weight basis, the range of doses reported to be effective clinically. When subcutaneous and intraperitoneal injections were made, the solution of sodium glutamate was injected in a concentration of 3 per cent (isomolar with body fluids) or 10 per cent. Because of the large volume of solution employed at the higher dose levels, control animals were given injections of a comparable volume of a solution of sodium chloride isomolar with the solution of sodium glutamate. In each type of experiment, in addition to controls, comparison was made of glutamic acid and one or more clinical or experimental anticonvulsants, such as phenobarbital, diphenylhydantoin, benzimidazole, Tridione (3,5,5-trimethyloxazolidine-2,4-dione) [4] and dimethyl-N-methyl barbituric acid.[4]

RESULTS

METRAZOL-INDUCED CONVULSIONS

Mice and Rats.—Twenty albino mice were given the solution of sodium glutamate by mouth in doses of 0.5 or 1 Gm. of the amino acid per kilogram of body weight. After from to two to five hours, a standard convulsant dose of metrazol (CD_{95+}), 85 mg. per kilogram of body weight, was injected subcutaneously.[5] Ten control mice were given the solution of sodium chloride by mouth in comparable volume and similarly received injections of metrazol. Single doses of glutamic acid had no discernible effect on the metrazol-induced convulsions. Indexes employed for comparison in these, and in subsequent, experiments included time of onset, character and severity of the convulsion and period required for recovery. Tridione and dimethyl-N-methyl barbituric acid, in doses not significantly depressant, are completely protective against twice the convulsant dose of metrazol.[6] The efficacy of phenobarbital and

3. The *l* (+) glutamic acid and diphenylhydantoin sodium were supplied by Dr. Oliver Kamm, of Parke, Davis & Company, Detroit.

4. These substances were supplied by Dr. R. K. Richards, of the Abbott Laboratories, North Chicago, Ill.

5. Goodman, L. S., and Lih, B.: Effect of Dilantin on Metrazol Convulsions, J. Pharmacol. & Exper. Therap. **72**:18, 1941. Lih, B.: The Protective Action of Dilantin Against Metrazol Convulsions, Thesis, Yale University School of Medicine, New Haven, Conn., 1941.

6. (*a*) Goodman, L. S., and Manuel, C.: The Anticonvulsant Properties of Dimethyl-N-Methyl Barbituric Acid and 3,5,5-Trimethyloxazolidine-2,4-Dione (Tridione), Federation Proc. **4**:119-120, 1945. (*b*) Goodman, L. S., and Toman, J. E. P.: Experimental Indices for Comparing the Efficacy of Compounds with Anticonvulsant and Antiepileptic Properties, ibid. **4**:120, 1945. (*c*) Everett, G. M.,

(Footnote continued on next page)

other barbiturates is well known. Single large doses of diphenylhydantoin are not anticonvulsant in this category of experiments.[5]

Inasmuch as certain anticonvulsant agents may not be effective clinically until medication has been carried out for several days, chronic experiments were conducted. Twenty albino mice and 10 albino rats were given sodium glutamate solution by mouth twice daily for five days, the single dose being 0.5 or 1 Gm. per kilogram of body weight. The standard convulsant dose of metrazol was then injected from two to five hours after the last dose of glutamic acid. For rats, this dose is 70 mg. per kilogram of body weight (CD_{95+}).[5] Control groups of 10 mice and 10 rats were intubated with comparable volumes of sodium chloride solution for five days and similarly tested with metrazol. Chronic treatment with glutamic acid did not modify the response to metrazol. Chronic therapy with diphenylhydantoin significantly reduced the incidence, severity and lethality of metrazol-induced convulsions in mice and rats tested as described here.[5]

Rabbits.—Three rabbits were prepared with epidural electrodes for electroencephalographic recording from both motor and occipital areas. Sodium glutamate solution was injected intraperitoneally and subcutaneously in doses of 0.5, 1 and 2 Gm. per kilogram of body weight, respectively, given twice daily for two days. From three to five hours after the first and the last injection electroencephalographic records were taken. Metrazol was then administered subcutaneously, 40 mg. per kilogram, and electroencephalographic recordings were made periodically. After injection of glutamic acid and before the injection of metrazol, the electroencephalographic record revealed no significant change from normal.

The electroencephalographic and motor responses to metrazol were in no way modified by glutamic acid, as revealed by control injections of metrazol in the same 3 rabbits and by comparison with numerous other controls. In contrast, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole, but not diphenylhydantoin, afford complete protection against the electroencephalographic and motor effects of convulsant doses of metrazol in rabbits.[7] Prior to the metrazol seizure, electroencephalographic responses occur in rabbits which simulate interseizure petit mal records in human subjects. Despite the reported clinical efficacy of glutamic acid for petit mal and psychomotor seizures, no

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and Richards, R. K.: Comparative Anticonvulsive Action of 3,5,5-Trimethyloxazolidine-2,4-Dione (Tridione), Dilantin and Phenobarbital, J. Pharmacol. & Exper. Therap. **81**:402-407, 1944; (*d*) Comparative Anticonvulsant and Hypnotic Action of Some Barbituric Acid Derivatives, Federation Proc. **4**:20, 1945.

7. Goodman, L. S.: The Pharmacodynamic Actions of Benzimidazole: A Preliminary Report, Bull. New England M. Center **5**:97-100, 1943. Goodman and Manuel.[6a] Goodman and Toman.[6b]

influence of the amino acid was detectable on the metrazol-induced petit mal type of dysrhythmia.

Cats.—Four cats were given glutamic acid intraperitoneally (0.25, 0.5, 1 and 4 Gm. per kilogram of body weight, respectively) and one to three hours later intravenous injections of 10 mg. of metrazol (CD_{90+}) per kilogram of body weight. Glutamic acid neither protected against nor modified the metrazol seizure. In contrast, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole but not diphenylhydantoin) completely prevent metrazol convulsions.[7a]

Monkeys.—In 3 monkeys (Macaca mulatta) control electroencephalograms and seizure responses to metrazol (50 to 90 mg. per kilogram) administered subcutaneously were established. One week later a solution of sodium glutamate (0.5, 1 and 2 Gm., respectively per kilogram of body weight) was injected subcutaneously and intraperitoneally. Metrazol was then given two to four hours after the glutamic acid and failed to alter the preconvulsive ("petit mal") electroencephalogram, the seizure electroencephalogram or the convulsion itself. In contrast, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole afford complete protection against convulsant doses of metrazol; diphenylhydantoin, however, is not protective.[7]

ELECTRIC SHOCK EXPERIMENTS

Rats.—Control thresholds averaged 28 milliamperes and varied from 24 to 36 milliamperes (0.2 second) in 10 rats. Sodium glutamate solution was injected subcutaneously in 3 groups of 2 rats each at dose levels of 0.25, 0.5 and 1 Gm., respectively, per kilogram of body weight. Two to five hours later the electric shock thresholds were found to be unaltered in all 10 rats. The 6 experimental rats were then given sodium glutamate for four days, the aforementioned single doses being repeated twice a day. The control rats were similarly treated with solution of sodium chloride. The electric shock thresholds were again determined within one to three hours after the last dose and were found unchanged. The character, severity and duration of the seizures were not modified . Phenobarbital Tridione and benzimidazole are capable of elevating the electric shock seizure threshold, but diphenylhydantoin is capricious and inconstant in this respect, such elevations as have been observed being insignificant in degree.[8] Tridione was given in large doses (400 mg. per kilogram, intraperitoneally) and sodium diphenylhydantoin both in single doses (50 to 100 mg. per kilogram,

7a. Everett and Richards.[6c,d] Goodman and associates.[7]

8. (*a*) Footnote 7. (*b*) Merritt, H. H., and Putnam, T. J.: A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, Arch. Neurol. & Psychiat. **39**:1003-1015 (May) 1938.

intraperitoneally) and in repeated smaller doses (25 to 50 mg. per kilogram, intraperitoneally twice daily for one week).

Two groups of 2 rats each were also tested with supramaximal currents (150 milliamperes, 0.2 second) one, two and five hours after receiving 3 and 6 Gm., respectively, of sodium glutamate per kilogram of body weight (divided equally between the oral, subcutaneous and intraperitoneal routes). The resulting maximal seizures were unaltered in severity, character and duration by the amino acid treatment. Other anticonvulsants abolish the tonic phase of the maximal convulsion.[9]

Cats.—A typical severe tonic-clonic seizure is produced in cats by supramaximal stimulation (300 milliamperes, 0.2 second). Single doses of glutamic acid given by mouth (0.5 to 1 Gm. per kilogram) or parenterally (4 Gm. per kilogram) did not alter the maximal seizures in 5 cats. Each cat had previously been tested with parenteral injections of phenobarbital (15 mg. per kilogram), diphenylhydantoin (10 to 40 mg. per kilogram), Tridione (400 mg. per kilogram) and dimethyl-N-methyl barbituric acid (100 to 125 mg. per kilogram); in every instance, the tonic phase of the seizure was completely obliterated. Furthermore, benzimidazole (350 mg. per kilogram) completely abolished the convulsion. These experiments and their significance will be reported in detail elsewhere.[9]

Rabbits.—Direct Cortical Stimulation: Epidural electrodes were implanted over symmetric areas of both hemispheres in 3 rabbits, to permit stimulation of the motor cortex on one side with single condenser shocks while the electrical activity of the opposite side is recorded. Thresholds were determined for primary and secondary electroencephalographic discharges [10] and for contralateral facial movements. Sodium glutamate in single doses of 1.5 Gm. per kilogram given intraperitoneally failed to alter these three thresholds significantly when tested at intervals up to three hours after injection and failed also to alter the typical wave form of the secondary discharge. In contrast, sodium phenobarbital (20 mg. per kilogram, intravenously) increased all three thresholds and altered the wave form of the secondary discharge. In minimally depressant doses, benzimidazole (100 mg. per kilogram, given intravenously) was more effective, and Tridione (400 mg. per kilogram, given intraperitoneally) less effective, than phenobarbital in raising thresholds. Diphenylhydantoin (60 mg. per kilogram, given intraperitoneally) was ineffective.

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9. Toman, J. E. P.; Swinyard, E. A., and Goodman, L. S.: Characteristics of Maximal Electroshock Convulsions: Their Modification by Drugs and Other Experimental Procedures, J. Neurophysiol., to be published.

10. Toman, J. E. P.: Cortical Responses to Cortical Stimulation in Relation to the Spontaneous EEG of the Rabbit, Federation Proc. **4**:72, 1945.

Monkeys.—A single oral dose of 0.5 to 1 Gm. per kilogram of sodium glutamate failed to alter the electric shock threshold in 4 monkeys (Macaca mulatta) or the duration or severity of the seizures. The control thresholds ranged from 34 to 52 milliamperes (5 seconds' stimulation). In all 4 monkeys the individual electric shock threshold remained constant within a variation of 10 per cent over a period of six months. Tridione and diphenylhydantoin in single large or in repeated small doses and dimethyl-N-methyl barbituric acid gave inconstant and capricious elevations in seizure thresholds (10 to 30 per cent). In contrast, phenobarbital and benzimidazole consistently elevated the electric shock convulsive threshold.

Hydrated Rats.—Rats hydrated by the oral administration of 4 doses of water at one-half hour intervals (5 cc. per hundred grams of body weight per dose) manifested a reduction in electric shock threshold of 36 to 76 per cent (average 56 per cent, 51 rats). Three pairs of rats, whose response to hydration was known, received orally 0.5, 1 and 2 Gm. per kilogram, respectively, of glutamic acid in acacia suspension. The electric shock threshold was retested thiry minutes after the last dose of water. The amino acid failed to protect against the lowering of threshold produced by hydration. In sharp contrast, phenobarbital, diphenylhydantoin, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole all elevated considerably the electric shock threshold lowered by this type of hydration.

A second type of hydration of brain tissue was accomplished by the technic of Darrow and Yannet,[11] which involves the intraperitoneal injection of isomolar solution of dextrose (5.5 per cent, 10 cc. per hundred grams of body weight) and its subsequent removal (250 to 280 minutes) after it has equilibrated with the extracellular fluid. The volume of fluid removed approximated that administered, so that total body water was not altered. By this means, nearly 40 per cent of extracellular electrolyte was lost to the body. Osmotic equilibration occurs through a shift of extracellular water into the cellular compartment. With employment of accepted values for distribution of body water and electrolyte, it can readily be calculated that cell volume may increase by 14 per cent. The "hydration threshold" (the electric shock threshold at the time of maximal cellular hydration) was reduced an average of 56 per cent (50 to 64 per cent, 24 rats). When glutamic acid in acacia suspension was administered to 4 rats in a dose of 0.5 or 1 Gm. by mouth and the procedure repeated as previously outlined, no significant change occurred in the hydration threshold. Quite dif-

11. Darrow, D. C., and Yannet, H.: Changes in Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, J. Clin. Investigation **14**:266-275, 1935.

ferent results were obtained when diphenylhydantoin, phenobarbital and Tridione were administered parenterally at a time which would allow their peak effects to become manifest coincident with the maximal reduction in electric shock threshold produced by hydration. The marked increase in hydration threshold caused by these three anticonvulsant agents and the inefficacy of glutamic acid are shown in the accompanying table.

It is apparent from the results obtained with glutamic acid in rats with brain cells hydrated by orally administered water or by experimental selective loss of extracellular electrolyte that the amino acid not only is incapable of elevating the electric shock threshold of normal

Inefficacy of Glutamic Acid in Lowering "Hydration Threshold" in Rats and Increase in Threshold Produced by Three Anticonvulsant Drugs

Rat No.	Rat Wt., Gm.	Volume 5.5% Dextrose Injected Intraperitoneally, Cc.	Time Between Injection and Paracentesis, Min.	Volume of Fluid Removed, Cc.	Concentration of Cation in Fluid Removed, mEq./L.	Amount Cation Removed per 100 Gm., mEq.	Normal Electric Shock Threshold, Ma.	Hydration Threshold After Paracentesis, Ma.	Decrease from Normal Threshold, %	Threshold After Amino Acid or Drug, Ma.*	Change from Hydration Threshold, %
1	300	30	255	29	126	1.22	30	14	53	G 12	— 14
2	284	28	260	27	126	1.20	36	14	61	G 16	+ 14
3	332	33	265	31	126	1.18	36	14	61	G 12	— 14
4	292	29	270	27	126	1.17	30	14	53	G 16	+ 14
5	316	32	250	32	126	1.28	30	12	60	D 18	+ 50
6	292	29	255	31	129	1.37	30	14	53	D 20	+ 43
7	288	29	255	28	135	1.31	26	10	62	T 20	+100
8	272	27	260	24	135	1.34	32	12	62	T 24	+100
9	340	34	280	33	135	1.31	24	10	58	P 18	+ 80
10	290	29	270	30	126	1.30	28	12	57	P 28	+133

* G indicates glutamic acid given orally in 10 per cent acacia suspension. For rats 1 and 2 the dose was 0.5 Gm. per kilogram of body weight; for rats 3 and 4, 1 Gm. per kilogram. D indicates diphenylhydantoin sodium, given intraperitoneally in a dose of 50 mg. per kilogram; T, Tridione, given intraperitoneally in a dose of 400 mg. per kilogram, and P, phenobarbital sodium, given intraperitoneally in a dose of 45 mg. per kilogram.

rats but is unable to protect against the lowering of threshold produced by hydration.

Toxicity.—Unna and Howe [12] reported salivation, vomiting and bradycardia after intravenous injection of large doses of glutamic acid in unanesthetized dogs. Madden and others [13] attributed to glutamic acid the toxic effects of amino acid mixtures and protein digests given

12. Unna, K., and Howe, E. E.: Toxic Effects of Glutamic and Aspartic Acid, Federation Proc. **4**:138, 1945.

13. Madden, S. C.; Woods, R. R.; Shull, F. W.; Remington, J. H., and Whipple, G. H.: Tolerance to Amino Acid Mixtures and Casein Digests Given Intravenously: Glutamic Acid Responsible for Reactions, J. Exper. Med. **81**: 439-448, 1945.

intravenously. To avoid these toxic effects, other routes of administration were used in our studies.

In rabbits, glutamic acid given intraperitoneally in doses of 1.5 Gm. per kilogram of body weight caused salivation, hyperpyrexia and impairment of placing reactions. Unexplained death occurred within several hours in 1 of 3 rabbits receiving 1.5 Gm. per kilogram and in both of 2 rabbits given 2 Gm. per kilogram of body weight. Even at this lethal level there was no evidence of anticonvulsant action of glutamic acid.

Cats were found to tolerate 4 Gm. per kilogram of body weight given intraperitoneally without toxic signs, but also without evidence of protection against metrazol or alteration in maximal electric shock seizures. In 1 animal given 8 Gm. per kilogram there developed salivation, hyperpnea and spontaneous tonic-clonic seizures, which increased in frequency and severity until death occurred, two hours after injection. Rats tolerated up to 6 Gm. per kilogram of body weight without toxic signs, but even at this high dose level there was no evidence of anticonvulsant activity. The largest doses given to monkeys (2 Gm. per kilogram of body weight) caused no alteration in temperature, respiration or neurologic signs.

COMMENT

The experiments here reported provide no indication of the mechanism of action whereby glutamic acid may exhibit its reputed suppression of petit mal and psychomotor seizures.[1] Although our laboratory indexes mainly concern major seizures, glutamic acid was also found ineffective against the petit mal type of electroencephalogram produced by subcutaneous injection of metrazol in rabbits and monkeys. Other drugs known to be more or less effective clinically in management of petit mal give positive protection against this experimental type of petit mal dysrhythmia in laboratory animals.

The two technics which appear to us to be most useful as laboratory devices for testing potentially anticonvulsant drugs are the supramaximal electric shock method [9] and the cellular hydration method, as employed in this study; the latter has been reported on in full elsewhere.[14] All clinically effective anticonvulsants except glutamic acid give positive results with these two technics. The cellular hydration method is of particular interest with regard to the question whether the electric shock seizure threshold is below normal in patients with epilepsy.[15]

14. Swinyard, E. A.; Toman, J. E. P., and Goodman, L. S.: The Effect of Cellular Hydration on Experimental Electroshock Convulsion, J. Neurophysiol. **9**:47-54, 1946.

15. Garciadiego, J.; Chávez, F. N., and Alcade, S. O.. Applicaciones del electro-choque como método de investigación y diagnóstico en los epilépticos, Arch.

(Footnote continued on next page)

Diphenylhydantoin, phenobarbital and Tridione are very effective in raising the threshold lowered by cellular hydration. Yet diphenylhydantoin is unable significantly to elevate the normal electric shock seizure threshold; this has been our consistent experience over a period of two years, employing rats, rabbits, cats and monkeys, and differs from the results of other investigators.[16] If it is true that known potent anticonvulsants in nondepressant doses cannot significantly elevate the normal electric shock threshold, then other laboratory methods of assay must be employed. The two suggested here seem most promising.

Since glutamic acid, even in large doses, showed neither anticonvulsant nor analeptic action with any of the methods employed, we are forced to conclude that its mechanism of action differs from that of all other clinical anticonvulsant agents. Investigations on the role of glutamic acid in cerebral metabolism and function [17] provide the basis for speculation on the possible nature of its action in epilepsy, but pertinent information is still lacking. One might postulate some subtle distortion of glutamic acid metabolism in patients suffering from petit mal. However, as Waelsch and Price [1b] pointed out, a daily protein intake of 70 Gm. provides 7 to 10 Gm. of natural glutamic acid, and the proteins of the body contain between 10 and 20 per cent of glutamic acid. By comparison, the doses of glutamic acid reported effective against petit mal (as little as 4.8 Gm. per day) seem almost superfluous.

SUMMARY

In an attempt to measure in the laboratory the anticonvulsant value of glutamic acid, this substance was tested by a number of technics

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de neurol. y psiquiat. de Mexico **7**:117-128, 1944. Kalinowsky, L. B., and Kennedy, F.: Observations in Electric Shock Therapy Applied to Problems of Epilepsy, J. Nerv. & Ment. Dis. **98**:56-67, 1943. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

16. Merritt and Putnam.[8b] Knoefel, P. K., and Lehrmann, G.: The Anticonvulsant Action of Diphenyl Hydantoin and Some Related Compounds, J. Pharmacol. & Exper. Therap. **76**:194-201, 1942. Tainter, M. L.; Tainter, E. G.; Lawrence, W. S.; Neuru, E. N.; Lackey, R. W.; Luduena, F. P.; Kirtland, H. B., Jr., and Gonzalez, R. I.: Influence of Various Drugs on the Threshold for Electrical Convulsions, J. Pharmacol. & Exper. Therap. **79**:42-54, 1943. Everett and Richards.[6e]

17. Krebs, H. A.: The Synthesis of Glutamine from Glutamic Acid and Ammonia, and the Enzymic Hydrolysis of Glutamine in Animal Tissues, Biochem. J. **29**:1951-1969, 1935. Nachmansohn, D.; John, H. M., and Waelsch, H.: Effect of Glutamic Acid on the Formation of Acetylcholine, J. Biol. Chem. **150**:485-486, 1943. Weil-Malherbe, H.: Studies on Brain Metabolism: I. The Metabolism of Glutamic Acid in Brain, Biochem. J. **30**:665-676, 1936. Zimmerman, F. T., and Ross, S.: Effect of Glutamic Acid and Other Amino Acids on Maze Learning in the White Rat, Arch. Neurol. & Psychiat. **51**:446-451 (May) 1944.

for investigating the potency of anticonvulsant agents. In a wide range of single large and repeated small doses, and in a variety of species, the amino acid was found ineffective in the prevention or modification of electrically or chemically induced convulsions. Glutamic acid failed to elevate the normal seizure threshold, did not modify the character of the convulsion produced by supramaximal currents and had no effect on the electric shock threshold lowered by cellular hydration. Glutamic acid was also without effect on metrazol-induced electroencephalographic dysrhythmias of the petit mal type. In addition, it did not alter the resting electroencephalogram or the electroencephalographic response to single cortical shocks.

Inasmuch as diphenylhydantoin, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole give laboratory evidence of anticonvulsant potency with one or more of the technics employed, it is suggested that if further clinical work substantiates the efficacy of glutamic acid in treatment of petit mal and psychomotor epilepsy the mechanism of its action is likely to prove considerably different from that of the known anticonvulsant drugs in clinical use. Indeed, one would not be able to predict from present laboratory screening methods that glutamic acid has anticonvulsant potency or value.

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SENSATION OF ELECTRIC SHOCK FOLLOWING HEAD INJURY

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RECENT observation of many cases of the sensation of electric shock on flexion of the neck as a result of war injuries has reawakened interest in this phenomenon, which was first noted and described during World War I. Heretofore it has been regarded as an interesting medical curiosity, chiefly because of its occurrence as a subjective symptom in cases of multiple sclerosis. Its appearance with this disease was described by Lhermitte, and the phenomenon is frequently referred to in the literature as "Lhermitte's sign." It is the purpose of this paper to report these recently observed cases, together with details of the variations of the symptom, for it is believed that this sign may be indicative of concomitant damage to the cord in cases of head injury and that it is of more than academic interest.

In an excellent brief review of the literature, Salmon [1] noted that in Babinski's neurologic service in World War I this phenomenon was observed in 12 cases; the data on these cases were abstracted by Ribeton [2] in his thesis published in 1919. Prior to this publication, however, Marie and Chatelin,[3] in 1917, reported a case of injury to the vertex and the occiput in which weakness of the arms was present, being more pronounced in the morning than in the evening, and in which flexion of the neck on the chest produced the sensation of an electric current running down both arms and legs. They noted that passive elongation of the brachial plexus gave the same response. Digital compression of the plexus caused pain in the shoulders and arms but did not produce the sensation of electric shock. They expressed the opinion that the cause of the phenomenon was an injury of the cervical

Capt. John A. Di Fiore and Capt. Glenn S. Player, of the Medical Corps, Army of the United States, assisted in the collection of the material on which this paper is based.

1. Salmon, L. A.: Sensation of Electric Shock in Multiple Sclerosis, Bull. Neurol. Inst. New York **6**:378, 1937.

2. Ribeton, J.: Étude clinique des douleurs à forme de décharge électrique consécutives aux traumatismes de la nuque, Thesis, Paris, no. 134, 1919.

3. Marie, P., and Chatelin, C.: Sur certains symptomes d'origine vraisemblablement radiculaire chez les blessés du crane, Rev. neurol. **24**:336, 1917.

roots by contrecoup. The next year Babinski and Dubois [4] reported the case of an officer with an injury of the neck who had the sensation of electrical discharge on the right side only. This officer showed a Brown-Séquard syndrome with right hemiparesis. Every time he flexed his neck he had an electrical discharge the length of his right arm and leg. The authors also mentioned 3 other cases of injury to the neck without signs of any damage to the cord in which the phenomenon occurred bilaterally. In commenting on these cases, Lhermitte expressed the opinion that the phenomenon was due to "cervical irritation." In 1918 Beriel and Devic [5] reported a case in which the sensation of electric shock was associated with multiple sclerosis. In 1924 Lhermitte, Bollack and Nicolas [6] described the sign as occurring early in the course of multiple sclerosis. This was followed by a second paper by Lhermitte and other collaborators,[7] with an excellent clinical description of the sensation by the patient herself. It was described as being like the recurrent ringing of a telephone bell, with electrical discharge lasting for three seconds on flexion of the neck and disappearing for four seconds. The discharge in this patient occurred not only on flexing her neck but on raising her head from flexion. It was never present during complete rest. For this reason, Lhermitte concluded that fatigue was a factor in the occurrence of the sign. He explained the phenomenon on the basis of early demyelination.

Since that time many cases of the phenomenon have been reported or discussed as a sign of multiple sclerosis (Roger, Reboul-Lachaux and Aymes [8]; Trioumphoff [9]; Wechsler [10]; Lhermitte [11]; Patrick [12]; Opalski,[13] and Read [14].

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4. Babinski, J., and Dubois, R.: Douleur á forme de décharge électrique, consécutives aux traumatismes de la nuque, Presse méd. **26**:64 (Feb. 4) 1918.

5. Beriel and Devic, E.: Sur un cas de douleurs à type de décharge dans la sclérose en plaques, Lyon méd. **141**:559, 1918.

6. Lhermitte, J.; Bollack, and Nicolas, M.: Les douleurs à type décharge électrique consecutives à la flexion céphalique dans la sclérose en plaques, Rev. neurol. **31**:56, 1924.

7. Lhermitte, J.; Lévy, G., and Nicolas, M.: Les sensations de décharge électrique: symptôme précoce de la sclérose en plaques, Presse méd. **35**:610, 1927.

8. Roger, H.; Reboul-Lachaux, J., and Aymes, G.: Dysesthésies rachidiennes à type de décharge électrique par flexion de la tête dans la sclérose en plaques, Rev. neurol. **1**:1052-1055 (May 31) 1927.

9. Trioumphoff, A.: A propos du symptôme de décharge électrique de la sclérose en plaques, Presse méd. **35**:948, 1927.

10. Wechsler, I. S.: A Case of Multiple Sclerosis with an Unusual Symptom, Arch. Neurol. & Psychiat. **19**:364 (Feb.) 1928.

11. Lhermitte, J.: Multiple Sclerosis: The Sensation of an Electrical Discharge as an Early Symptom, Arch. Neurol. & Psychiat. **22**:5 (July) 1929.

(Footnotes continued on next page)

Data on Thirty Patients Experiencing Sensation of Electric Shock as Result of Head Injury

Patient No.	Location of Injury; Size	Onset of Symptom After Injury	Duration of Symptom	Distribution of Sensation	Other Symptoms	Comment
1	Left temporal defect, 4 by 4 cm.	4 wk.	3 mo.	Left side of neck and left arm	Transient weakness of left arm	Sensation disappeared before insertion of tantalum plate
2	Left frontoparietal defect, 4 by 4 cm.	4 wk., immediately after clearing up of weakness of arms	5 mo.	Spine and both arms	Weakness of both arms for month after injury	Epidural hemorrhage found at operation; plate inserted 4 weeks after injury
3	Left temporal defect, 3 by 2.5 cm.	8 wk.	3 mo.	Chest, arms and thighs	Transient numbness of fifth fingers of both hands for 3 days after injury	No loss of consciousness
4	Linear fracture, right temporal region	7 wk.	2 mo.+*	Neck; anterior and posterior thoracic walls to D 4; both arms, D 6	None	Unconscious for 10 days; homonymous diplopia on looking to right, and vertigo
5	Left temporoparietal defect, 4 by 4 cm.	11 wk.	7 wk.	Arms, posterior and anterior thoracic walls	Mild weakness of left arm still present	.....
6	Left parietal defect, 4 by 4 cm.	15 wk.	5 wk.	Left side of neck, left arm and fingers.	Transient numbness in distribution of left ulnar nerve	Electric sensation disappeared immediately after insertion of tantalum plate
7	Left temporal defect, 2 by 1.5 cm.	9 wk.	2 mo.+*	Left anterior chest wall left arm, left third, fourth and fifth fingers of left hand	Objects in left hand dropped on flexion of neck	Sensation not momentary but lasting 1-3 seconds.
8	Left postauricular region; no fracture	3 wk.	5 mo.+*	Spine, arms and legs	Initial transient paralysis of both arms; now weakness of both arms, increased by flexion of neck	Shock on jugular compression; momentary weakness of hands and sensory diminution on flexion of neck
9	Right occipital defect, 4 by 4 cm.	3 wk.	2½ mo.	Finger tips of both hands	None	Residual left homonymous hemianopsia; deafness and tinnitus on right
10	Left temporal defect, 2.5 cm.; dura not lacerated	2 mo.	6 mo.	Spine, both arms and hands	None	Sensation not momentary but may last 2-3 minutes if neck if kept flexed
11	Right frontal defect, 3 by 5 cm.	13 wk.	1 mo.	Spine and legs	None	Sensation lasts 2-3 seconds.
12	Left occipital defect, 4 by 5 cm.	10 days	5 mo.	Both hands	None	Electric shock lasts 2 minutes; recovery from right homonymous hemianopsia
13	Defect in left frontal lobe, 3 by 3 cm.; fragment in left occipital lobe, 0.5 by 0.3 cm.	3 mo.	2 mo.	First left arm and fingers; 2 weeks afterward right arm and fingers	None	After disappearance of shock on flexion of neck, sensation of electric shower in left finger tips on washing hands with water
14	Left parietal defect, 7 by 7 cm.	1 mo.	7 wk.	Anterior wall of chest, abdomen, legs	None	Sensation not momentary but lasts 3 seconds; worse at night

15	Loss of left eye; simple fracture of right parietal bone	2 mo.	1 mo.	Left arm, sternum to umbilicus	None	Shock not consistent; jugular compression diminished intensity of shock
16	Right frontal defect, 4 by 4 cm.	6 mo.	6 mo.	Sensation felt deep in abdomen at level of umbilicus	None	No recurrence of electric shock since disappearance, 7 months ago
17	Left frontoparietal defect	1 wk.	13 mo.+*	Both arms, anterior wall of chest and epigastrium	None	Shock extremely weak and inconstant now but not completely gone
18	Right occipital defect, 4 by 2.5 cm.	3 mo.	8 wk.	Ascending from neck to posterior portion of scalp	Left homonymous hemianopsia, tinnitus	.....
19	Left temporal and left occipital defects, each 4 by 4 cm.	2 mo.	Disappearance from legs in 2 mo. and suddenly from rest of body in 3 mo.	Both arms, trunk and legs; continuous on flexion of neck; persists for hours; not painful	Memory defect	Meningitis present; 11,020 cells per cu. mm., 86 per cent polymorphonuclear cells; no organisms; treatment with sulfathiazole and intrathecal administration of penicillin
20	Right parietal defect, 6 by 6 cm.	3 mo.	3 mo.	Only down spine	Left hemiparesis; transient numbness of right hand and foot; left hemianopsia; position and vibration senses impaired in left fingers and toes	Shock sensation lasts 2 seconds; all neurologic signs cleared up except slight weakness of left leg
21	Anterior left frontal defect, 2.5 by 3 cm.; posterior left frontal defect, 1.5 by 2 cm.	3 mo.	1 mo.+*	Neck, shoulders and spine but not arms	None	.....
22	Right occipital injury; no fracture	3 mo.	2 wk.*	Anterior wall of chest and both arms	None	Complete retrograde amnesia for 12 weeks; recovery
23	Simple fracture of left occiput	3 mo.	1 mo.*	Starts at spinous process of D 8 vertebra, ascends to both shoulders and goes down both arms	None	Injury to left ulnar nerve 12 years ago; electric shock sensation does not radiate in distribution of left ulnar nerve
24	Right temporal craniotomy; removal of meningeal fibroblastoma	5 mo.	2 wk.	Left side of forehead, face and neck; left arm and left leg	Left hemiplegia and hemianopsia, improved after removal of tumor	Electric shock sensation produced only by flexion of trunk
25	Left frontoparietal defect, 3 by 3 cm.	6 mo.	1 wk.	Both arms	None	Sensation accidentally discovered on shaking of head; flexion did not produce sensation
26	Left parietal defect, 6 by 4 cm.	11 mo. after injury and 1 wk. after recurrence of aphasia	1 wk.	Ascends from right great toe up right side of body to face	Right spastic hemiparesis and hemihypalgesia	Sensation stimulated by tapping dorsum of right great toe
27	Left temporoparietal defect, 6 by 6 cm.	2 mo.	1 mo.*	Left hand and fingers, mostly palmar	Patient recovering from right hemiplegia and asphasia	.....
28	Bifrontal and left temporal defects	2 mo.	1 mo.*	Lateral aspect right arm; inner aspect of right forearm and right fifth finger	Patient recovering from right hemiplegia	Arm most involved in paralysis
29	Left frontoparietal defect	2 mo.	1 mo.	Entire right side of body from face down	Right hemiparesis and hemihypalgesia; recovery	Sensation stimulated by jugular compression and bending of trunk
30	Left frontoparietal defect, 4 by 8 cm.	6 wk.	2 mo.	Right arm from deltoid surface to palm, mostly along medial surface	Recovery from right hemiplegia	Sensation disappeared immediately after cranioplasty

* Sensation of electric shock still present at time of writing.

Patrick mentioned that the phenomenon has also been observed in cases of tumor of the spinal cord and of tuberculosis of the cervical vertebrae. In 1933 Olkon [15] and Hassin [16] each described the sign in a case of subacute combined degeneration of the cord. Hassin's case had the advantage of being studied pathologically, and the typical, well known characteristics of that pathologic entity were found. This author took issue with Lhermitte as to the explanation of the phenomenon and stated that he doubted whether early demyelination is the answer, since demyelination occurs late and the sign usually appears early in the disease. He expressed the opinion that the sign might be due to swelling of the spinal nerve fibers. He stated:

> Additional factors are probably at play; either special sets of nerve fibers are affected or the destructive process is especially severe.

Neither process can be proved pathologically. In his review of the literature and in his paper reporting 6 cases, Salmon [1] stated the opinion that the sign may be a late as well as an early one in multiple sclerosis.

During World War II attention was first called to this sign in a paper recently published by Triumfov,[17] who was the author of a paper previously mentioned.[9] In a report of 23 cases of injury to the brain he stated that the intensity of the symptom is related to the nearness of the wound to the foramen magnum and that the sensation is usually more intense in the extremities on the side of the injury. In most of the cases the histories suggested to Triumfov that meningeal irritation, probably on the basis of hemorrhage into the meninges and roots, was the cause. It was usual for the symptoms to develop at the time of healing of the wound or two or three weeks later. He assumed the formation of scar tissue and adhesions in the meninges. The symptom developed and disappeared gradually. Its usual duration in his series was one to two months.

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12. Patrick, H. T.: The Symptom of Lhermitte in Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:1075 (May) 1930.

13. Opalski, A.: Accès paralytique (décharge paralytique) dans un cas de sclérose en plaque, Rev. neurol. **38**:281, 1931.

14. Read, C. F.: Multiple Sclerosis with Lhermitte's Sign, Arch. Neurol. & Psychiat. **27**:227 (Jan.) 1932.

15. Olkon, E. M.: Subacute Combined Degeneration with Symptom of Lhermitte in "Pernicious Anemia" Case, J. Nerv. & Ment. Dis. **77**:256, 1933.

16. Hassin, G. B.: Paraplegia in Flexion and the Symptom of Lhermitte, Arch. Neurol. & Psychiat. **29**:855 (April) 1933.

17. Triumfov, A. V.: The Symptom of "Electrical Discharge" in Brain Injuries, Am. Rev. Soviet Med. **2**:350, 1945.

ANALYSIS OF CASES

The table presents an outline of the data on 30 patients recently observed in an Army general hospital, all of whom had suffered head injuries. The subjects ranged in age from 19 to 38 years. Some were not unconscious at all after their injury. The longest period of unconsciousness was ten days. Some of the patients had no neurologic sequelae; others had severe hemiplegia, from which recovery took place slowly. Twenty-five of the patients had comminuted fractures, with resultant defects in the skull of sizes indicated in the table. Three of the patients showed only simple linear fractures, and 2 had no roentgenographic evidence of skull fracture. The sites of the bony injuries and damage to the brain in these patients were as follows: frontal, 4; frontoparietal, 5; temporal, 6; temporoparietal, 2; parietal, 5, and occipital, 4. Two patients had double defects—1, temporal and occipital, and the other, bifrontal and temporal. Twenty of the fractures occurred on the left side. A review of the cases indicates that the site of the lesion is probably not a factor in the production of the symptom.

The appearance of the phenomenon of electrical discharge varied from a few days to six months after the injury, the average time being nine weeks. At the time of this writing some of the patients are still experiencing the phenomenon. In most, however, the symptom has disappeared. The average duration for the patients in whom the sensation no longer exists was a little over three months.

All patients who did not describe an unequivocal sensation of electrical discharge were not considered. Patients who described tingling, numbness and tingling, or vibration were rejected for inclusion in this series. It was surprising that in many instances the patients spontaneously described this symptom, and in several it was the chief complaint, since it kept them from being comfortable; 1 patient was awakened from sleep at night because of the pain involved. Except in the cases to be mentioned specifically later, the description was a classic one: On flexion of the neck there was a momentary sensation of electric shock, which started in the neck and passed down the arms, spine and legs. Variations were numerous; in some patients the phenomenon was one sided, although bilaterality was more frequent. In most patients the electric shock was an invariable sequel to flexion of the neck. In the others it occurred only occasionally on flexion. In all patients the onset of the symptom was sudden. In a few its disappearance was sudden. For the most part, however, the disappearance was gradual. This brief summary indicates already some differences in the symptomatology in this series from that in Triumfov's. Except when indicated in the separate case reports, roentgenograms of the cervical portion of the spine and studies of the spinal fluid showed a normal condition.

Group 1.—Analysis of the case material reveals no clearcut evidence that the single factor of concussion of the cervical portion of the cord is the chief determinant in production of the sign. However, for 7 of the patients (1, 2, 3, 5, 6, 7 and 8) the weight of the evidence certainly tends to confirm the original impression of Babinski and Dubois [4] that the phenomenon is due to damage to the cervical part of the cord by contrecoup. This evidence was deduced from the cases in which signs of damage to the cervical portion of the cord immediately followed the injury. Patient 1, for instance, had transient weakness in the left arm after an injury to the left temporal area, and he later experienced the phenomenon only in the left side of the neck and the left arm. Patient 2 suffered weakness of both arms for a month after an injury to the left frontoparietal area, and the discharge of electrical phenomenon appeared in his spine and in both

arms as his weakness began to clear up. Patient 3 had transient numbness of the fifth finger of both hands for three days after his head injury. The sensation of electrical discharge appeared eight weeks after his injury and lasted for three months in his chest, arms and thighs. Patient 6 had transient sensory loss in the distribution of the left ulnar nerve, and fifteen weeks after his injury a sensation of electric shock developed in the left side of his neck, in his left arm and in the fingers of his left hand.

As can already be noted, signs of both sensory and motor involvement referable to the cervical portion of the cord were in evidence in these patients. Careful study showed that this weakness was of the type referable to the cervical portion of the cord rather than due to involvement of the cerebral cortex. Patient 7 had excellent motor power in the left hand after a defect in the left temporal area of the skull and involvement of the left temporal lobe, from which he had recovered. Nine weeks after the injury the sensation of electric shock developed in the left anterior portion of the chest, the left arm and the third, fourth and fifth fingers of the left hand. If while holding something in his left hand he flexed his neck, the object would drop from his hand because of the sudden, but momentary, weakness.

Patient 8 showed the most extensive involvement of the cord. This soldier was struck in the left postauricular region by a swinging steel hook. He immediately fell unconscious. When he regained consciousness, within an hour, he had complete paralysis of both arms. An hour later he was able to move his arms, but the weakness persisted. Gradually it cleared up so that his power was about 80 per cent normal. Sensory examination showed definite diminution of all modalities of sensation from the fourth to the eighth cervical segment. Three weeks after the head injury he began to notice a sensation of electric shock which passed down both arms, the spine and both legs. On flexion of the neck, there was an increase in the weakness in his hands, and he occasionally dropped objects which he was holding. Also, he reported that momentarily, for the duration of the shock, which was not particularly disconcerting, there was an increase in numbness. This could be tested and was best discernible with vibratory sense. He was the only patient studied in this series in whom the sensation of electric shock could be initiated by jugular compression; with this procedure he received the same momentary sensation of shock. It is, perhaps, worth while to note that roentgenologic studies showed no evidence of fracture of the spine or the skull. Studies of the spinal fluid revealed a normal condition. Since all these patients received their injuries in combat and immediate surgical intervention was available for them, there was no particular indication for studies of the spinal fluid; hence there are no reports on such studies done at the time of the injury. Examinations of the spinal fluid which are reported on here are those made at the time of study, usually months after the injury. In case 8, however, an examination of the spinal fluid was done immediately after the injury, and there was no evidence of any abnormality.

Group 2.—According to the opinions expressed by various authors, the patients in the first group all presented a condition in which there is neurologic evidence of injury to the cord concomitant with the head trauma. In the next group to be considered (patients 4, 9, 10, 12, 13, 19, 22, 25 and 27) symptoms not unlike those of the first group were presented, but there was no direct evidence of sensory or motor changes in the upper extremities. On the basis of similarity of the nature and distribution of the sensation of electric shock, it is likely that the etiologic factor is the same. Yet it must be noted that variations in the dis-

tribution were more evident. In patient 4, for instance, the sensation of electric discharge had a segmental distribution from the second cervical to the fourth dorsal segment, and along the sixth dorsal segment, skipping the fifth dorsal segment.

Patient 9 experienced the phenomenon only in the finger tips. In patient 10, previously mentioned, in whom the sensations were so intense as to cause awakening from sleep, the phenomenon was not momentary but would last as long as three minutes. Also, for reasons unknown, there were periods of two or three days in which the phenomenon could not be elicited at all by any means. It would then reappear and last for two or three days. The patient, "a health addict," found that after a series of Turkish baths the sign disappeared entirely for ten days. On discontinuation of the baths the attacks resumed their usual frequency and intensity, to diminish gradually as time went on.

How complex and variable the phenomenon may be is illustrated by case 13. The soldier was struck by a shell fragment in the left frontal region; after débridement, a defect measuring 3 by 3 cm. was left in that region. Roentgenographic examination showed a small fragment lodged in the left side of the occiput. This soldier had right hemiplegia, aphasia and right homonymous hemianopsia. At the time of this writing he has recovered completely from his aphasia, his hemiplegia has almost entirely disappeared and only the hemianopsia remains. Three months after his head injury, on flexion of the neck, the sensation of electric shock appeared in his left arm and the fingers of his left hand. Two weeks later the phenomenon appeared in the right arm and fingers and was then bilateral. Two months after its appearance the sensations on flexion of the neck began to disappear and within a few weeks were completely gone. The phenomenon disappeared from the right side more quickly than it did from the left. During this period of subsidence the patient noted that if his left hand came in contact with water sensations of electric shock occurred in the finger tips of the left hand, but after a week they also disappeared. After this, however, he noted that if he rubbed his face with his left hand when he was bearded and needed a shave, tingling would appear in the finger tips. The phenomenon could be elicited only over the bearded portion of the face, and only in the left hand. The last-mentioned subjective symptom of tingling was not the same as the phenomenon of electric shock. This soldier showed roentgenographic evidence of lipping of the anterior margin of the sixth cervical vertebra, which was interpreted as evidence of mild arthritis and as having nothing to do with the phenomenon under discussion.

In another unusual case, that of patient 19, details of the nature of the injury are not clear, but it seems from the medical records available that the soldier suffered a bullet wound the point of entrance of which was the left temporal region and the point of exit the left occipital region. In both these areas he had defects in the skull measuring 4 by 4 cm. On arrival at this hospital, two months after his injury, he had pronounced amnestic aphasia and he had no memory whatever for events prior to his injury. Since then he has gradually recovered much of his pretraumatic history. On his admission, it was noted that there was slight bulging of both cranial defects and that he had a low grade fever. Spinal tap revealed the presence of 11,000 cells per cubic millimeter, with 86 per cent polymorphonuclear cells. On treatment with sulfathiazole and intrathecal administration of penicillin the cell count dropped to about 450 per cubic millimeter, all of which were lymphocytes. The spinal fluid pressure was very low. At the time of writing, he still has occasional low grade fever. Organisms have never

been cultured from the spinal fluid. The cause of the patient's meningitis remains a diagnostic problem, and various explanations have been offered, including that of sterile abscess. He is free of complaints.

After the initiation of the antimeningitis therapy, the patient became aware of sensations of electric shock on flexion of his neck. They occurred in both arms and ran down the entire body and both legs. The sensation of shock continued as long as the neck was kept flexed and disappeared only when it was extended to a normal position. The sensation was not painful. After two months the sensation of electric shock on flexion of the neck began gradually to disappear in his legs, and after three months it disappeared from the entire body.

It is clear that in the two large groups delineated here nerve pathways mediate the electric discharge. Additional confirmation is gathered from case 23. The soldier had had an accident in civilian life, resulting in partial palsy of the left ulnar nerve. After his head injury and the development of the phenomenon of electric discharge he experienced the sensation down both arms but not along the sensory distribution of the left ulnar nerve.

Group 3.—Seven of the cases (11, 14, 15, 16, 17, 20, and 21) are placed together because it is difficult to explain the distribution of the electric discharge via anatomic nerve pathways. The radiation down the spine and legs in patient 11 can be explained anatomically, but the more common radiation down the arms was absent. Patient 14 had, besides his cranial injury, minute metallic bodies just above and posterior to the spinous process of the sixth cervical vertebra; surprisingly, the electric discharge did not radiate down his arms but only down the anterior thoracic wall, the abdomen and both legs.

Patient 15, for instance, felt the shock in his left arm and fingers, but it also traveled down the sternum and anterior abdominal wall in a narrow strip to the level of the umbilicus. Patient 15, curiously, felt the sensation of shock deep within the abdomen at the level of the umbilicus, and at no time did he have the sensation anywhere else. The longest duration of the sensation in any patient of this series was that in patient 17, who still experiences the phenomenon, though definitely diminished in intensity, after thirteen months. Interestingly, the period after injury at which his sensations began was the shortest in the series. Patients 20 and 21 also had unusual distributions of the electric discharge; the one only down the spine and the other down the neck, shoulders and spine.

Group 4.—The usual course of the electric discharge was downward. In 3 patients this direction was reversed. In patient 18 the discharge began in the posterior part of the neck and ascended, to be felt in the posterior half of the scalp; the area involved was fairly congruent with the distribution of the second cervical spinal nerve. An unusual course of the discharge occurred in patient 23, in whom the sensation began at the spinous process of the eighth dorsal vertebra, ascended to the neck and then descended down both shoulders and arms.

Patient 26 was struck by numerous shell fragments in the left parietal region, and several fragments could not be removed at operation. Sequelae to his injury were right spastic hemiplegia, expressive aphasia and a right hemisensory syndrome. Eleven months after his injury the aphasia and sensory changes had disappeared and the hemiplegia had improved to the point at which he could walk with the aid of a cane. One night he indulged heavily in alcoholic beverages. He experienced a sudden headache; his motor aphasia recurred, and the hemiplegia became severe, so that he became bedridden. Jacksonian twitchings of the right side of the face appeared. Examination of the spinal fluid showed nothing abnormal. Two days later his aphasia began to clear, and he complained of strangeness of feeling on the right side of the body, especially in the hand. The

right arm and hand often felt as though they did not belong to him. Pain, touch and temperature senses were impaired on the right side. Position sense was absent from the right hand but not from the toes. This exacerbation lasted a week and then recovery was rapid. During the week of sensory disturbance it was discovered that tapping the ball of the right great toe with a reflex hammer initiated sharp electric shock which ascended from the toe up the foot, leg and thigh, the right side of the abdomen and chest and the right shoulder, down the right arm and up the right side of the neck. The face was not involved. The electric sensation could not be elicited by any other means.

Group 5.—Though the clinical picture presented by patient 26, just described, does not fit into the usual pattern of the phenomenon under discussion, it provokes interest in the possibility of cerebral involvement as a major etiologic factor in some cases. The cases of 4 other patients appear, from their clinical course, to constitute a group in which this may be true.

Patient 24, a 24 year old soldier, suffered from headaches and gradually diminishing vision. At operation a meningeal fibroblastoma filling the entire right middle fossa was successfully removed. After the operation he had left hemiplegia and hemianopsia, but his condition gradually improved. Five months after the right temporal craniotomy he noted sensations of electric shock on flexion of the trunk. The sensation of shock began in the left side of the forehead, descended down the left side of the face and neck and the left arm and leg, skipping the thorax and abdomen. The symptom persisted two weeks.

The case of patient 26 was described in the preceding group. The electric discharge was present only during the acute encephalopathic episode and then disappeared, thus being suggestive of an intimate causal relationship.

Patient 28 suffered a bifrontal and left temporal injury, with right hemiplegia, involving chiefly the arm. Two months after his injury there developed the sensation of electric discharge down the right arm and forearm and the fifth finger.

Patient 29 suffered right hemiparesis and hemihypalgesia, from which he recovered. During the period of recovery and for two months after his injury, on bending the trunk he experienced the phenomenon of electric shock down the entire right side of his body, beginning with the face. The sensation could also be elicited on jugular compression.

Patient 30, likewise, while recovering from right hemiplegia, experienced the sensation of electric discharge down the right arm. The phenomenon disappeared immediately after cranioplasty and the insertion of a tantalum plate.

An additional case, not listed in the table, exemplifies another variation of the phenomenon which appears best explained on the basis of a cerebral factor. The 21 year old soldier was struck by a mortar shell fragment in the left frontoparietal region . He was not unconscious and never had any complaints. At operation the dura and brain were found to be lacerated, but only slightly. Ten weeks after the injury he had a cranioplasty, and a tantalum plate was inserted over the defect. One month later, while lying in bed, he experienced a sudden, severe shock at the site of the injury. The sensation of shock spread rapidly over the entire body and lasted about two seconds. It was experienced most strongly in the posterior part of the neck, where it was painful. Three nights later and one week later identical attacks took place. There have been no similar episodes since. The soldier said that the shock was as though a live electric wire were placed on his head at the site of the injury and operation and the electric current ran through his entire body. No motor phenomena accompanied the sensations.

COMMENT

The clearest discussion of the possible explanation of the phenomenon is that given in a review of the subject by Lhermitte.[18] He stated that since the phenomenon can be caused by passive flexion of the neck without contraction of muscles or effort, and since it occurs with multiple sclerosis, subacute combined disease of the cord and injuries of the cord, the most likely explanation lies in the pathologic process common to all these conditions, namely, recent demyelination. The sensation of shock is not unlike that experienced by patients with peripheral nerve injuries, known as Tinel's sign. Therefore Lhermitte mentioned this phenomenon as an analogous situation in which a similar pathologic condition exists. When one considers how forceful a trauma some of these soldiers have sustained, as in the case in which a missile entered the left temporal region and made its exit from the left occipital region, it is not at all surprising that the same force could have damaged the cord. This concomitant injury of the cervical portion of the spine and of the cord in association with head injuries has of course been noted before in the literature. It was recently emphasized by Walshe.[19] In the present series, all cases in group 1 and most of the cases in group 2, are suggestive of concomitant concussion of the cord. Many cases of group 3 and cases 18 and 23, of group 4, may also fall into this category.

To the various discussions on the pathophysiology of the condition this series of cases, unfortunately, does not add much except to stress that whether or not the process is one of demyelination it is definitely reversible. The overwhelming number of cases of open head injuries (in this series, 25 with defects of the skull and only 5 with closed injuries) cannot be without significance. Since undoubtedly bleeding is present in the open wound, some weight is thrown toward support of Triumfov's hypothesis that a causative factor may be meningeal adhesions around nerve roots following bleeding. Yet in only a few cases in group 1 were there signs of radiculopathy, and there was in no instance any clinical picture resembling adhesive arachnoiditis.

In consideration of the possibility of meningeal adhesions another hypothesis presents itself. Could the presence of adhesions at the site of the defect, where in most instances there was laceration of the brain and dura, fixate the brain, so that flexion of the neck caused an extension of the cervical portion of the cord and irritation of the

18. Lhermitte, J.: Le signe de la décharge électrique dans les maladies de la moelle epinièré. Le signification semiologique, Gaz. d. hôp. **106**:1017, 1933.

19. Walshe, F. M. R.: Note on a Commonly Unrecognized Type of Injury to the Cervical Spine and Spinal Cord in Association with Head Injuries, Lancet **2**:173, 1944.

cervical roots? Nothing conclusive can be deduced from this series in answer to this question except that in 2 cases (6 and 30) the sign disappeared immediately after cranioplasty.

The cases in group 5 argue for an overwhelming cerebral factor in the production of the phenomenon. Whether one should go so far as to postulate a separate cerebral center for perception of electical sensation is doubtful. Yet such a hypothesis might be ventured, since both perceptual and inhibitory centers for qualitative sensations related to the phenomenon of electric discharge are being discovered.[20] Whether in this connection the large number of left-sided lesions (in two thirds of the cases) is a factor is conjectural. Nor is the fact that in several cases the phenomenon could be produced by bilateral jugular compression or by bending of the trunk considered evidence for or against either the hypothesis of a cerebral origin or that of concussion of the cord.

Attempts to correlate the symptoms with the site of the lesion, the duration of unconsciousness and the nature and time of operative intervention have failed. Triumfov's observations that the symptom is usually experienced on the same side of the body as the head injury and that an injury in the parasagittal region leads to bilateral perception of the symptom are not corroborated by the evidence in this larger group of cases.

Since Lhermitte stated in several papers that in his opinion the phenomenon may be due to actual generation of electricity, studies with the neurodermometer were made in a series of these cases. In no instance could a change in electrical resistance of the skin be detected with this instrument during the phenomenon. Use of the electroencephalogram, in an attempt to pick up "electrical currents" with electrodes along the course of the "discharge," failed to produce any deviation during the production of the sensation.

SUMMARY

A series of 30 cases of head injury is presented in which the phenomenon of sensation of electric shock was perceived in various parts of the body on flexion of the neck. Multiple etiologic factors may be operative; the hypothesis of concomitant concussion of the cord and of a special cerebral origin are discussed. The pathologic process is unknown, demyelination of spinal tracts and meningeal scars being considered as likely factors; the process, however, is self-limited and reversible so far as the phenomenon is concerned.

74 Perry Street, New York 14.

20. Yacorzynski, G. K., and Davis, L.: Studies of the Sensation of Vibration, Arch. Neurol. & Psychiat. **53**:355 (May) 1945.

NEUROPSYCHIATRIC OBSERVATIONS ON TSUTSUGAMUSHI FEVER (SCRUB TYPHUS)

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ALTHOUGH records indicate that tsutsugamushi fever (scrub typhus, Japanese river fever, kedani fever, Japanese flood fever) has been known to exist for over a thousand years, the American medical profession had little experience with the disease until it was encountered among troops stationed in certain areas of the Southwest Pacific theater of the war. Tsutsugamushi, which is caused by Rickettsia nipponica (Rickettsia orientalis, Rickettsia tsutsugamushi), is widely distributed over an area which includes Japan, Malaya, French Indo-China, Sumatra, the Philippines, other islands of the Pacific and northern Australia. The disease will continue to be brought to the attention of physicians in the United States by returned soldiers who have residual manifestations and may again be encountered among the occupation troops in the islands of Japan.

Numerous clinical investigations have been made since the first description of tsutsugamushi by Palm, in 1878. Although frequent references to neurologic and psychiatric manifestations of the disease have been made, no adequate study of the lesions of the central nervous system has been published. The present report is based on observations on a group of American soldiers and Marines during an outbreak of the disease on Goodenough Island in the D'Entrecasteaux group, off the northern coast of the eastern tip of New Guinea.

GENERAL CLINICAL OBSERVATIONS

Fifty-one patients were studied. The most common presenting complaints were severe frontal headache, malaise, anorexia, nausea and vomiting. Every one of these patients had headache. All but 5 had anorexia. Twenty-eight had nausea, and 22 had vomiting. An eschar was demonstrable in 39 patients. The course of the disease showed great variability. Bronchial symptoms with a nonproductive cough; pneumonia; faint heart sounds; evidences of mild renal involvement; enlargement and, often, tenderness of the liver and spleen; generalized

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lymphadenopathy, especially prominent in the regional nodes draining the site of the eschar; maculopapular eruption; congestion of the vessels of the conjunctiva and leukopenia were common features. Some presented tachycardia, while others showed a relatively slight elevation of pulse rate considering the degree of fever. Sustained elevations of temperature, of from 104 to 105 F., and sometimes rising to 106 or 107 F., lasted from ten to fourteen days. Two patients had a terminal rise to 108 F. Of the 39 patients whose serum gave a Weil-Felix reaction with the OXK strain of Proteus vulgaris, 35 had agglutinations in dilutions of 1 : 80 or above.

The variation in the clinical course is illustrated by case studies.

CASE STUDIES

CASE 1.—This case is characteristic of the mild form of the disease, with rapid and complete recovery.

A man aged 35 had an onset characterized by eschar, headache, nausea and tinnitus. The course of the disease was mild. The temperature did not rise above 103 F. The Weil-Felix reaction was positive in a dilution of 1 : 1,280 on the fourteenth day. On getting out of bed he had considerable dizziness and weakness. His weight had fallen from 175 to 155 pounds (79.5 to 70 Kg.). He steadily gained in strength and weight. Although he had no delirium and seemed fairly clear during the acute phase of his illness, he stated that for several days "things seemed hazy" and that he later did not remember what happened during this period. Two months after the onset of his illness he had no residual manifestations.

CASE 2.—This case illustrates the severe headache, prostration, deafness, tinnitus and mental depression commonly encountered. Recovery was slow but complete.

A man aged 26 first became sick on Nov. 24, 1943, and his illness ran a stormy, acute course. He had an eschar on the penis, generalized lymphadenopathy, anorexia, prostration, maculopapular rash, deafness, tinnitus, bilateral bronchopneumonia and delirium. Generalized edema lasted for several days. His weight fell from 155 to 130 pounds (70 to 59 Kg.). On December 2, while he was semidelirious, his headache was very severe. Symptomatic relief was obtained by the slow withdrawal of 15 cc. of cerebrospinal fluid, which was under increased pressure, contained 11 mononuclear cells per cubic millimeter and gave a 1 plus Pandy reaction. By Jan. 20, 1944 he had regained 10 pounds (4.5 Kg.), slept well and had amnesia for the acute phase of his sickness. He felt depressed and was easily irritated. On May 7, after returning from a sick furlough in Australia, he felt well except for slight tremor of the hands and lack of "pep and energy." In August 1945 there was no evidence of residual symptoms.

CASE 3.—Prolonged delirium was followed by persistence of difficulty in concentration and interference with original thinking eighteen months after the acute phase of the illness.

A man aged 27 was taken sick on Nov. 18, 1943. He rapidly went into a delirium, during which he talked of swimming and lying on the bottom of the ocean. At times he felt that he had died and that his wife had collected his $10,000 insurance. Cheyne-Stokes respirations appeared, and severe, prolonged hiccups were present. By December 8 he was in an apathetic state and remarked

that he did not care whether he lived or died. During the next two months he felt weak, experienced difficulty in concentration and expressed feelings of unreality. In March 1944 he went to the mess hall and did not discover that he had left his mess gear in the ward until he returned from dinner. On contemplating what had happened, he then realized that he had had a cup of coffee instead of a complete meal. While on sick furlough, in March and April, his strength and thinking capacity improved. Feelings of unreality disappeared. When interviewed on May 7, he had the following symptoms: lack of energy and ambition, headaches and dizziness in the morning, slowness of thinking, mildly defective memory and diminished capacity to carry out original and imaginative thinking. Although he formerly had been able to write articles in Polish for a newspaper, the thoughts he put on paper were silly and disconnected. (He had spoken no English until he came to the United States, at the age of 22.) In March 1945 he felt that he had not recovered completely. He noted difficulty in concentration and in writing simple letters, was restless, lost his temper easily and felt that his powers of original thinking had deteriorated.

CASE 4.—This case illustrates severe neurologic involvement and clouding of the sensorium. Eighteen months after the illness there were persistence of weakness in the legs and defect in grasp of complicated thought.

A man aged 38 had a severe, acute illness with a temperature of 105 F. It was characterized by intractable headache; nausea; vomiting; deafness; impaired vision; bronchopneumonia; muscular weakness; Cheyne-Stokes breathing; pains in the ocular muscles, legs and arms; diminution of sensation to touch, pain, position and vibration in the lower extremities; hyperactivity of knee and ankle jerks; hiccups; urinary incontinence, and delirium. There was a hard, smooth, hemorrhagic patch around the limbus of the left eye. The fundus of the right eye showed a small periarterial hemorrhage on the nasal side. On recovering from the acute phase of his illness, he ate well but continued to complain of pains and weakness, particularly in the legs. He spoke of the acute phase of his illness as follows: "For three weeks I had strange feelings and did not know anything. I thought I was a prisoner and tried to get away. I got out of bed several times. I had an idea my body wasn't whole and my legs were separated. I heard bells ringing." Eighteen months later he noted weakness in the legs, slowness of thinking and difficulty in grasping complicated thoughts.

CASE 5.—This case was characterized by severe neurologic and psychiatric symptoms with recovery except for easy fatigue and memory defect.

A man aged 25 had a severe febrile stage of his illness without evidence of pulmonary or cardiac complications. It was characterized by difficulty in swallowing, in enunciation and in extending his tongue. The jacket used to shade a lamp was interpreted as a piece of fresh meat, and an attempt was made to secure it. A railroad train with hungry people, a beautiful Australian girl and cows and pigs as passengers was seen traveling under his mosquito net. At times he had muscular twitching. For three weeks evidences of neurologic involvement persisted. For several months he continued to feel weakness in his legs and to have mild feelings of unreality and difficulty in memory and concentration. Eighteen months after the acute phase of his illness he noted easy fatigue and interference with recent memory.

CASE 6.—The case was characterized by delirium, which persisted after the febrile stage, and features of a Korsakoff syndrome, with residual thinking difficulty and feelings of unreality.

A 22 year old private in the Marine Corps had a severe febrile phase of the illness, lasting two weeks, and delirium, persisting for a week after the fever had subsided. For several weeks he had pains in the legs. He was taken sick on Dec. 8, 1943. Shortly after admission he began to feel that he had been moved from one ward to another. He had ideas that he had wandered from the hospital to the beach, where he fixed an airplane, flew to a recently invaded island, strafed the Japs and prepared the way for the landing of the Marines. He wrecked his plane, escaped by submarine assisted by a Chinese boy, sank much Jap shipping, lost his submarine, escaped in another boat to Goodenough Island, bought and distributed fresh foods with the help of fuzzy-wuzzies, carried out various exploits in a Marine Corps airplane, was made a major in the air corps and was so successful that he was promoted to be a three star admiral, in command of the battleship North Carolina. A prominent movie star was executive officer. The patient's temperature returned to normal on Jan. 3, 1944, but evidences of disorientation, defective memory and confabulation persisted. By the end of January he had considerable insight into his mental abnormalities but had difficulty in concentration and frequently saw images of people. This he appreciated as unusual. For many years he had been interested in boats and airplanes. He realized that his ideas about flying and sailing were determined by his hobbies. He was anxious to discuss the origin of the delusions and was greatly relieved as he gained insight into them. By the middle of April he felt well physically but had some difficulty in thinking and periods when his surroundings seemed unnatural.

Case 7.—This case illustrates a severe course, with slow disappearance of neuropsychiatric symptoms and persistence of tachycardia and pain in the left upper abdominal quadrant, which may have been secondary to a splenic infarct.

A man aged 24 was taken ill on Dec. 4, 1943. His illness had a severe, febrile course with delirium, tachycardia, faint heart sounds, rales at the bases of both lungs and severe pain in the left upper quadrant. Anorexia persisted for several weeks. His weight fell from 192 to 160 pounds (87 to 72.6 Kg.). During his delirium he became frightened, thought that he was constantly walking with a beautiful girl and was suspicious that the personnel of his organization had turned against him. After subsidence of the delirium, he experienced violent nightmares of running away from Japs or Indians, of being chased by an old woman and of climbing an endless staircase. He had episodes of irritability, generalized trembling and excessive sweating. By the middle of February 1944 he was feeling well except for difficulty in remembering several things at one time. For example, when he had to deliver charts to two wards, it required great effort to keep in mind the numbers of these two wards. He gained in strength and alertness during a sick furlough to Australia, lasting from March 2 to April 6, 1944. There was a return of sexual desire, the loss of which had caused him considerable concern for two months. Six months after the onset of his illness he had difficulty in concentration, slowness in thinking, tachycardia and pain in the splenic region. By August 1945 he felt well physically except for persistence of the pain in the left upper quadrant. His resting pulse was 110 a minute. He had continued at duty as a guard. He felt that he was not so sharp in originating thought as he had been before his illness. "I now grope for words. At one time I was president of a debating team and had no trouble with my speech or writing. I sleep lightly now. I used to sleep very soundly. Until four months ago I had nightmares about a man sticking a knife in me and spilling out my intestines. I would get up, put on a light and look around my tent for him."

CASE 8.—This case serves to illustrate a severe, fatal type of the disease complicated by meningitis. The characteristic pathologic changes of tsutsugamushi were found.

A man aged 23 had a severe reaction, which ended in death on the twelfth day after his admission. His illness began on April 3, 1944 with frontal headache and an eschar in the right suprapubic region. By April 5 he had a fever, slight chill, urinary frequency, photophobia, generalized muscular aches, pain on movement of his eyes and a slight, nonproductive cough. Physical examination on his admission, on April 6, showed congestion of the vessels of the conjunctivas, a temperature of 100.2 F. and a necrotic, punched-out lesion surrounded by a red areola several millimeters in diameter. Generalized lymphadenopathy was noted. The white cell count was 4,900. A maculopapular rash developed on the chest and back. Six days after his admission respiration became labored and cyanosis appeared. Rales were found in both pulmonary fields. Hearing was impaired. Granular casts and albumin were found in the urine. On April 13 the Weil-Felix reaction was positive in a dilution of 1 : 40, and on April 17, in a dilution of 1 : 320. By April 15 he had severe hiccups, frequent extrasystoles and a pulse rate of 130 a minute. He became restless and irrational. He remarked that he seemed to "hear double" and that he could see his mother, father and fiancée. He had an overwhelming desire to escape from Goodenough Island, which he particularly disliked. He seemed frantic. A lumbar puncture was done, with withdrawal of 15 cc. of fluid, under slightly increased pressure. It contained 17 mononuclear cells per cubic millimeter, and the total protein measured 29 mg. per hundred cubic centimeters. The next day the patient became excited and overtalkative; his temperature rose to 105 F.; his pulse and blood pressure were unobtainable, and the illness terminated fatally.

Postmortem examination [1] showed diffuse inflammatory changes in many organs. In the lungs there were extensive dilatation of blood vessels and invasion of the alveolar walls with lymphocytes and histiocytes. The cardiac muscle fibers appeared pale, and there was infiltration of lymphocytes and histiocytes between bundles. The pulp of the spleen was hemorrhagic; many large histiocytes were seen, and erythrophagia was demonstrable. The hepatic cells were granular, and diffusion of histiocytes, lymphocytes and occasional polymorphonuclear leukocytes was seen throughout all areas and in clumps around the portal units. In the kidneys the inflammatory reaction was minimal and limited to infiltration of rare mononuclear cells in interstitial areas. The testes showed thickening of the basement membranes of the seminiferous tubules, only immature cells in spermatogenesis, congestion of the interstitial spaces and extensive infiltration with histiocytes and lymphocytes. The lymph nodes showed congestion, indistinct markings and sinusoids containing histiocytes and lymphocytes.

NEUROLOGIC AND PSYCHIATRIC MANIFESTATIONS

The involvement of the central nervous system in tsutsugamushi has been described [2] as characterized by severe giddiness and headache and later in the disease by hyperesthesia over the body, delirium at night and deafness.

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1. Lieut. Col. Vernon L. Lippard, of the Medical Corps, provided the report on the pathologic examination.

2. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942, p. 981.

Reynes and Richard,[3] after guinea pig inoculation, isolated the rickettsia bodies from the cerebrospinal fluid. Their patient was delirious, noisy, incontinent and hiccuping. Neurologic examination revealed tremors of the face and extremities and absence of knee and ankle jerks. Three days later hiccups disappeared, and the patient presented a syndrome of spasticity with generalized hyperreflexia. After a further brief period of delirium with erotic content he recovered except for amnesia for events which occurred during and after his illness. The cerebrospinal fluid contained 14, 30 and 137 cells per cubic millimeter on three examinations. The Weil-Felix reaction with the OXK strain of P. vulgaris was positive in a dilution of 1 : 150. Ragiot and Delbove [4] reported diffuse cerebral involvement, particularly in the midbrain. Poinso [5] found stupor and delirium and selective involvement of the gray matter of the bulb and pyramidal tracts.

In epidemic typhus, which has similar pathologic lesions, severe symptoms referable to the central nervous system have been observed. Von Stockert [6] reported somnolence, auditory hallucinations and catalepsy, followed by restless delirium. The patient passed into a dream state, and became convinced that he had received a high decoration from the hands of Hitler. Von Stockert also noted that months after defervescence there may be serious mental disturbances, such as changes in disposition or appearance of criminal tendencies and that mental deterioration of the type found in encephalitis may be permanent.

In the present series of patients the most frequent evidences of neurologic involvement were deafness, in 34; ringing in the ears, in 26; generalized or localized bodily pains, in 25; pain on movement of the eyes, in 18; urinary incontinence, in 17; muscular twitching, in 17; impairment of vision, in 17; hiccups, in 10; meningismus, in 5, and urinary retention, in 3. Both hypoactivity and hyperactivity of the tendon reflexes were observed. Respiration was abnormal in most cases. It was usually rapid, the rate frequently rising to 40 per minute. Nine patients, of whom 5 recovered, had Cheyne-Stokes breathing. Other symptoms which were noted in a few patients were convulsions, dysphagia, dysarthria, strabismus, inequality of the pupils, nystagmus,

3. Reynes, V., and Richard, J.: Sur un cas de typhus tropical à forme nerveuse, Bull. Soc. path. exot. **33**:70-73 (Feb. 14) 1940.

4. Ragiot, C., and Delbove, P.: Trois cas de manifestations nerveuses au cours des fièvres typho-exanthématiques observées en Cochinchine, Bull. Soc. path. exot. **29**:839-844 (Oct.) 1936.

5. Poinso, R.: L'encéphalite boutonneuse, Presse méd. **47**:1159-1161 (July 26) 1939.

6. von Stockert, F. G.: Die psychischen Störungen bei Fleckfieber, Deutsche med. Wchnschr. **69**:506-508 (July 9) 1943; abstracted, Trop. Dis. Bull. **41**:201-202 (March) 1944.

inability to protrude the tongue, hyperesthesia, anesthesia and partial to complete loss of sense of touch, pain, position and vibration.

One patient who had severe neurologic manifestations on recovering from coma had intractable pins and needles sensations in his legs. Examination showed diminished sense of touch and hypersensitivity to pinprick in his feet and slightly hyperactive tendon reflexes and loss of position and vibration senses in his lower extremities. These symptoms gradually subsided over a period of several weeks. In another patient there were transient loss of position and vibration sense; severe burning in the soles of the feet, lasting about three weeks, and feelings of numbness in the left thigh, which persisted for about five weeks. Acute parkinsonism occurred in a man who had lost much weight.

Wolf [7] found localized myopathy occurring in 2 patients with tsutsugamushi disease during the acute phase and persisting for many months thereafter. The muscular weakness and atrophy in both patients occurred about the shoulder girdle and exhibited the characteristics of muscular dystrophy of the Landouzy-Dejerine type.

The cerebrospinal fluid of 8 patients was examined. That of 1 patient was entirely normal. In 2 patients the only abnormality was a slight elevation of its pressure. In 1 patient (case 6) the fluid contained white blood cells and 15 red blood cells per cubic millimeter. Another (case 2) had a Pandy reaction of 1 plus and a cell count of 11 mononuclear cells per cubic millimeter. For a patient who died, the results of examinations of the spinal fluid were recorded as follows: (1) mononuclear cells 3 per cubic millimeter; (2) xanthochromic fluid, a Pandy reaction of 1 plus and 35 mononuclear cells per cubic millimeter; (3) a Pandy reaction of 1 plus and 5 mononuclear cells per cubic millimeter. In the fluid of another patient (case 8) who died 17 mononuclear cells per cubic millimeter were found. For a severely ill patient who survived the following values were reported: 40 mononuclear cells per cubic millimeter, a Pandy reaction of 2 plus and a total protein content of 70 mg. per hundred cubic centimeters.

Cerebral function was impaired in almost every patient. Symptoms varied from periods of apathy and restlessness to severe prolonged delirium followed by residual thinking difficulty. Thirty-one patients had poor concentration; 30, loss of memory; 29, delirium, and 17, coma. Disorientation was found in 34 patients. Twenty-four had delusions, and 17 had hallucinations. One patient had a Korsakoff psychosis. During convalescence, illusions, feelings of unreality and *déjà vu* phenomena were noted. Some were emotionally complacent throughout

7. Wolf, S.: Myopathy: Localized Muscular Weakness with Atrophy of an Unusual Type Occurring Among American Soldiers in the Southwest Pacific, to be published.

their illness. Twelve showed definite fear and many others some degree of anxiety. Seventeen were depressed, and 7 had marked irritability.

As in other conditions with toxic or anatomic involvement of the central nervous system, the personality background and emotional reactions of the patient influenced the thought content. Conflict was manifested by fears of a Japanese attack, of injury to self or comrades or of disaster at home involving financial problems, deaths or infidelity of wife or sweetheart. Those who had been in combat frequently relived battle experiences. Paranoid ideas of being mistreated, robbed or killed were expressed. A Marine who had taken part in the difficult campaign at Guadalcanal had delusions that he was on the Russian front wondering what he was going to do next. Distorted ideas often were based on the immediate situation. For example, when there was profuse sweating, the patient felt that he was floating on a lake, being sprinkled with dew, swimming in the ocean or being placed in a damp hole. One man who was not allowed visitors felt that all men in his organization had turned against him. With some, reality problems were overcome or wishes fulfilled. An Alabama farmer thought he was happily driving a team of mules. A man who had been overseas for over two years felt he was visiting friends and relatives. Another was having a lively time at night clubs accompanied by his fiancée, who appeared to be unusually beautiful and well dressed. Some heard sweet, soothing music. A patient who was especially weary of canned food, of the prohibition of liquor and of the heat of the tropics during a delirium felt that he was on a cool boat going to Australia on furlough and was surrounded by a plentiful supply of beer and delicious food.

In cases of the milder form of the disease, in which there was no gross evidence of abnormality during the febrile stage of the disease, there were later periods of loss of memory, ranging from one to seven days. In cases of the more severe form there was amnesia for as long as four weeks. Manifestations referable to the central nervous system commonly persisted after the acute phase of the illness. During the severe delirium there was less variation in symptoms between day and night than in the febrile delirium which complicates such diseases as pneumonia and typhoid. In a few patients previously existing psychoneurotic tendencies, such as anxiety, depression and hypochondriasis, were accentuated. In many there was a loss of sexual feeling. It is likely that this was due to general debility. The frequent testicular involvement, with soreness, flabbiness and pain, called the patients' attention to their genitalia and created anxiety about their sexual function.

Although there were few in the series of 51 patients who showed psychoneurotic symptoms of any consequence, another group, of 20

patients, who had previously been hospitalized for tsutsugamushi fever at other locations in New Guinea, later came to the Ninth General Hospital, where definite manifestations of an anxiety state, hysteria, neurasthenia or hypochondriasis were found. They knew that other soldiers, who had survived the disease, had been returned to the United States as patients. Most of them had acquired the disease months before and had been in many hospitals. In their travels from place to place they had been subjected to various philosophies in regard to the proper management of their illness, had picked up much misinformation and had had ample opportunity to misinterpret the points of view to which they had been exposed. Many of their symptoms were similar to those they had experienced during the acute and the convalescent stage of tsutsugamushi. Common complaints were easy fatigue, weakness, headaches, anxiety, palpitation, tremulousness, diffuse pains and excessive somatic preoccupation. There was usually a history of a remission followed by an exacerbation when the patient was confronted with unpleasant or dangerous army duties. Some responded well to psychiatric treatment, but others did poorly, particularly those with rigid personality patterns.

The severity and dramatic nature of the symptoms and the high mortality had a terrifying effect on the men who had been exposed to the disease but did not contract it. During the outbreak at Goodenough, three or four times the usual number of men reported on sick call. Most of them were suffering from mild anxiety and hypochondriacal reactions, which subsided as soon as the incidence of the disease decreased.

PATHOLOGIC CHARACTERISTICS

In 1936 Lewthwaite and Savoor [8] noted petechial hemorrhages in the heart, lungs, alimentary tract and kidneys and small perivascular infiltrations in the pons, medulla and cerebellum. The cells surrounding the blood vessels were reported as neuroglia cells and lymphocytes, and rickettsias were thought to have been demonstrated in the cells of the walls of blood vessels. Thrombus formation was noted in some of the capillaries. Wolbach [9] pointed out the presence of areas of necrosis in various organs and suggested that small blood vessels of the internal organs may present lesions leading to thrombosis.

In this series, postmortem examination was made in 13 cases. In 2 cases no abnormalities of the central nervous system were noted. In 3 cases there was edema of the brain with flattening of the convolutions.

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8. Lewthwaite, R., and Savoor, S. R.: Typhus Group of Diseases in Malaya, Brit. J. Exper. Path. **17**:1-34 (Feb.) 1936.

9. Wolbach, S. B., in Virus and Rickettsial Diseases, Harvard School of Public Health, Symposium, Cambridge, Mass., Harvard University Press, 1940.

There was moderate congestion of the cerebral vessels in 3 cases. Hemorrhages into the leptomeninges were found in 4 cases. In 1 case (8) meningitis developed. Lesions similar to those found in other organs of the body were noted in the central nervous system on microscopic examination. The blood vessels were congested. There were necrosis of the media of arterioles and a perivascular infiltration of monocytes and lymphocytes. Thromboses were in various stages of early organization. Some of the neurons showed degeneration. In several cases in which the central nervous system showed no severe involvement there was a severe complicating bronchopneumonia.

Microscopic sections from case 8 were examined by Dr. S B. Wolbach, professor of pathology at Harvard Medical School, who gave the following opinion:

> I find focal lesions in the cerebellum, cerebral cortex, pons and thalamus. They are of the same general character as those associated with typhus. In this particular case they are fewer and much less abundant in the pons than with typhus, but, as in cases of typhus, there must be a great variation in distribution. The infiltration of the meninges is of about the same degree and character as with typhus, the majority of the cells being mononuclear leukocytes or monocytes. I have compared these lesions with those in typhus, and they are so similar that I am quite certain that a fairly extensive study would be necessary to bring out any differences. Certainly, any differences in cellular composition and relation of the infiltrations to capillaries and vessels of precapillary size would be quantitative, rather than qualitative. I should conclude, therefore, that the involvement of the central nervous system bears the same relation to the signs and symptoms of tsutsugamushi fever as do the lesions of the central nervous system of Rocky Mountain spotted fever and typhus to the signs and symptoms of these diseases.

PROGNOSIS

The fatality rate has shown much variation in different outbreaks. Dyer [10] reported it as about 15 per cent for persons of all ages. The prognosis is poorer with increase in age.

Evidence of severe involvement of the central nervous system during the acute phase of the disease signified a poor prognosis. Of 17 patients who were in coma, 5 recovered. Thirteen (25 per cent) of the 51 patients died. Of the 38 survivors, follow-up data were obtained by means of interview or report by letter after six months for 25 patients and after eighteen months for 24 patients. It was possible to follow 16 men closely because they were members of this hospital detachment. Nineteen of the 24 patients had continued on duty in the Pacific area. The other 5 patients had been returned to the United States for the following reasons: length of overseas service, 1; malnutrition, 1; psy-

10. Dyer, R. E.: The Rickettsial Diseases, J. A. M. A. **124**:1165 (April 22) 1944.

choneurosis, 1; and an unknown reason, 1. The 2 patients with psychoneurosis had had severe emotional difficulties of many years' duration, for which they had received treatment in Army hospitals prior to contracting tsutsugamushi fever. All 24 patients were able to carry on useful work either in the Army or in civilian life.

After six months 12 patients and after eighteen months 17, including the 2 with psychoneurosis, showed no residual manifestations. The 7 patients of the 24 (29 per cent) who continued to have symptoms complained of poor concentration, memory defect, decreased ability to grasp complicated ideas, difficulty in original and imaginative thinking, easy fatigue, deafness, tremor of the extremities, pains and weakness in the legs, tachycardia, pain in the testes and splenic region and dyspnea on exertion. One patient said, "My mind feels partly withered away." Another reported, "I feel just like a burnt-out motor." Some of these symptoms may have been psychogenic. However, for the most part they were present continuously and appeared to be secondary to severe organic involvement at the time of the acute phase of the disease. When emotionally determined symptoms were not recognized and treated, chronic psychoneurotic reactions frequently developed. If recovery was incomplete after six months, the outlook for further improvement was poor. Sexual feeling returned to normal after the debilitating phase of the illness was passed. In addition to residual manifestations referable to the central nervous system cardiovascular symptoms, such as tachycardia, precardial discomfort and dyspnea, sometimes persisted.

TREATMENT

Since there is no specific treatment, symptomatic and supportive care is of the greatest importance. The value of convalescent serum, which was given in several cases, was questionable. Oral administration of adequate quantities of liquids as judged by the state of hydration of the patient and the urinary output seemed best in these cases. A well balanced diet of simple foods as tolerated was important in order to maintain the nutrition and strength of the patient. Tactful spoon feeding by nurses or ward men was of great help. Morphine, scopolamine and paraldehyde were the drugs of choice in the control of restlessness and insomnia. When there was evidence of severe, intractable headache, small amounts of cerebrospinal fluid were withdrawn gradually in order to give relief. During the delirium the environment was simplified as much as possible in order to lessen the bewilderment of the patient. The number of persons caring for the patient was kept at a minimum, and visitors were restricted. Simple explanations and reassurance helped to decrease perplexity and fear. During convalescence analysis of the significance of the delusional ideas increased

the ease and confidence of the patient. Care was taken to insure gradual increase of physical and mental activity in accordance with the patient's tolerance. It may be necessary to have the patient under medical supervision for as long as six months. Attention to the personality as a whole was of value in helping the patient to return to useful work as soon as he is capable of it. Brief analysis of personality reactions, explanation of the disease and of its symptoms, reassurance and encouragement were of benefit in many cases.

COMMENT

In tsutsugamushi fever one is dealing with a generalized disease which may be accompanied with mild to severe involvement of the central nervous system. Neurologic and mental examinations indicate functional and structural change in the cerebrum, the brain stem and the spinal cord. In some cases the neurologic signs point exclusively to peripheral involvement. These may be the result of nutritional deficiency and may be similar to those seen in other severe or debilitating illnesses. Inadequate caloric intake together with high fever resulted in loss of weight, sometimes as high as 60 pounds (27 Kg.). The period of convalescence was frequently prolonged, and recovery was sometimes incomplete. The persistence of symptoms suggested that they were due to parenchymal destruction and secondary gliosis. Personal communication with physicians in other locations in the New Guinea area where tsutsugamushi is a common disease indicated that an unusually severe form of the disease was observed at Goodenough Island and that the manifestations of involvement of the central nervous system were more prominent than in outbreaks in other cases. The cause, symptoms and pathologic changes are similar to two diseases about which more is known, namely, Rocky Mountain spotted fever and epidemic typhus.

SUMMARY

Neuropsychiatric observations were made on a group of 51 patients with tsutsugamushi fever during an outbreak on Goodenough Island. Mortality was 25 per cent. All patients exhibited involvement of the central nervous system, manifestations ranging widely from transient toxic cerebral symptoms to evidence of severe, widespread inflammation, resulting in coma and death. Pathologic changes in the central nervous system were similar to those found in other organs of the body and consisted of focal lesions characterized by necrosis, thrombosis and perivascular infiltration with numerous mononuclear cells, lymphocytes and plasma cells and rare polymorphonuclear leukocytes. The rate and degree of recovery varied considerably. Twenty-nine per cent of

patients on whom follow-up data were available, eighteen months after the acute phase of the disease, showed residual manifestations, most of which appeared to be secondary to organic changes of the central nervous system. None had symptoms of sufficient severity to prevent performance of useful work. During the acute illness symptomatic treatment and good nursing care were of major importance. During convalescence graduated activity under medical supervision and prompt treatment of psychoneurotic manifestations facilitated recovery. Psychotherapy, with a brief analysis of personality reactions, explanation, reassurance and encouragement, was found to be of benefit.

New York Hospital.

PERMEABILITY OF BLOOD-SPINAL FLUID BARRIER IN INFANTS AND IN NORMAL AND SYPHILITIC ADULTS

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POSITIVE Wassermann reactions rarely occur in the spinal fluid in the absence of syphilitic involvement of the central nervous system. "False positive" reactions of the spinal fluid have been observed [1] in patients with meningitis of bacterial or virus origin, especially in persons with a positive Wassermann reaction of the serum, and it has been assumed that the normal barrier between the blood and the central nervous system may be impaired by the meningeal inflammation, permitting the passage of reagin from the serum into the spinal fluid. The positive Wassermann reactions of the spinal fluid of these patients reversed after the symptoms of meningitis subsided.

Lately, we examined the spinal fluid of 16 newborn infants with syphilis. In 4 infants the results were completely normal; in 4 a positive Wassermann reaction with a high cell count, a high protein value and an abnormal colloidal gold curve were found and a diagnosis of syphilitic involvement of the central nervous system was made. In 8 infants moderately positive Wassermann reactions were found, while the cell counts, protein values and colloidal gold curves were normal; these observations are not unusual in patients with long-standing or well treated neurosyphilis and are commonly interpreted as evidence of inactivity of the infection. In the newborn, however, one cannot assume that a "burnt-out," long-standing neurosyphilis has caused reagin to remain in the spinal fluid while all other signs of an active

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1. Scott, V.; Reynolds, F. W., and Mohr, C. F.: Biologic False Positive Spinal Fluid Wassermann Reactions Associated with Meningitis, Am. J. Syph., Gonor. & Ven. Dis. **28**:431 (July) 1944.

inflammation have subsided. These 8 infants showed a high reagin titer in the serum, the Wassermann reactions being positive in dilutions of from 100 to 300, while the spinal fluids gave positive reactions with 1 and 0.6 cc. and negative reactions with 0.4 cc. This pattern is suggestive of a passive transfer of reagin from the blood into the spinal fluid.

The 4 infants for whom a diagnosis of neurosyphilis was made were treated with sulfarsphenamine in the usual dosage and showed an unexpected quick reversal of all abnormal features of the spinal fluid. Adults with early syphilis, exhibiting a pattern of the spinal fluid abnormal in all respects, do not respond quickly to therapy and require at least a year or more for complete reversal to normal. These

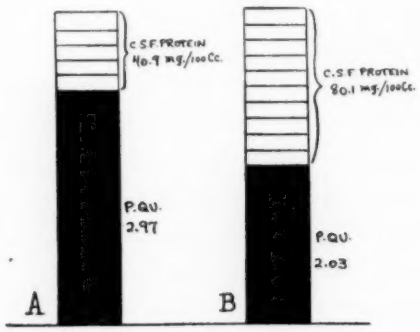

Fig. 1.—Graph showing the relation of the total protein content of the cerebrospinal fluid to the permeability quotient (*P. Qu.*) of the barrier between the blood and the cerebrospinal fluid for patients with neurosyphilis (*B*) and for normal (control) adults (*A*). The average permeability quotient of normal patients and of patients with neurosyphilis is in inverse ratio to the amount of total protein, expressed in milligrams per hundred cubic centimeters.

4 infants, however, showed a completely normal spinal fluid within a short period. The case of 1 of these infants is reported in brief.

J. F., a French-Canadian girl, was admitted to the Children's Memorial Hospital in Montreal at the age of 2 months in a critical condition. The liver and spleen were palpable; there was severe diarrhea, and the temperature was elevated to from 101 to 103 F. A widespread, maculopapular eruption was noted, with moist papules about the anus and genitals, and brownish red, shiny infiltrations were present on the palms and soles. There were hypertrophic papules on the tongue and a purulent nasal discharge. The pupils did not react to light; the eyes did not follow moving objects, and the child appeared to be blind; ophthalmologic examination revealed prominent, edematous nerve heads. The child could not move the right arm; there was a pronounced swelling of soft tissue about the right parietal bone, and roentgenographic examination revealed destructive changes of the proximal ends of both radii, osteochondritis, zones of rarefaction, periostitis

of the long bones and a zone of rarefaction on the right parietal bone. The Wassermann reaction of the blood was positive in a dilution of 1 : 256. The mother was syphilitic. A diagnosis of congenital syphilis, with cutaneous, mucosal and skeletal involvement, and syphilitic neuritis of the optic nerve was made.

The general health improved quickly with transfusions, dietary adjustment and mild antisyphilitic therapy. The child was discharged after two months, completely free of symptoms and with apparently normal vision. While she was in the hospital, a total dose of 750 mg. of sulfarsphenamine was given. Therapy with sulfarsphenamine and a bismuth compound was continued for one year at the treatment center of the Royal Victoria Hospital; on completion of therapy, the spinal fluid was normal in all respects, and the Wassermann reaction of the blood was negative.

The rapid improvement in the condition of the spinal fluid reflects the favorable clinical course. The laboratory data were as follows:

Date	Cells per Cu. Mm.	Pandy Reaction	Protein Content, Mg. per 100 Cc.	Wassermann Reaction	Colloidal Gold Curve
12/28/43	95	+	123	+ with 0.2 cc.	Not determined
1/ 9/44	75	+	77	+ with 0.2 cc.	1 1½ 2 2 2 2½ 1 0 0 0
3/ 8/44	2	—	27	— with 1.0 cc.	Normal

The unusually quick reversal of the spinal fluid to normal in this case may be explained by assuming that the arsenical level in the spinal fluid of very young children treated with trivalent arsenicals is higher than that in adults because the barrier between the blood and the spinal fluid is undeveloped.

The relation of the spinal fluid to the blood has been treated in an exhaustive and masterly way by Katzenelbogen[2] in his monograph which contains a complete bibliography up to 1936. He cites the following work: Stern and Peyrat found that crystalloids pass freely from the blood into the spinal fluid in newborn animals in which the central nervous system does not reach maturity at birth, such as dogs, cats, rats, mice and rabbits, and that as the animals grow the resistance of the barrier gradually increases. The newborn guinea pig shows the same permeability of the barrier at birth as does the mature animal. Robinson found a high permeability of the barrier in newborn mice in which trypan blue was injected subcutaneously; this permeability gradually decreased as the mice grew older. Few such observations have been made on human subjects. Lenov noted increased permeability to uranium in children during the first years of life. Kruse, using Walter's bromide method, found a high perme-

2. Katzenelbogen, S.: The Cerebrospinal Fluid and Its Relation to the Blood: A Physiological and Clinical Study, Baltimore, Johns Hopkins Press, 1935.

ability in 16 of 28 children less than 3 months of age, while in older children values identical with those of adults were noted.

These reports and our clinical observations, previously noted, indicated that a comparison of permeability of the barrier in infants and in normal and syphilitic adults at various stages of the disease might be of interest.

PRESENT INVESTIGATION

The bromide permeability test, devised by Walter,[3] was used, chiefly because it has been extensively employed in studies of patients with neurosyphilis; this test is designed to demonstrate a normal, an increased or a decreased permeability of the blood–spinal fluid barrier. Sodium bromide is given by mouth, 0.02 Gm.

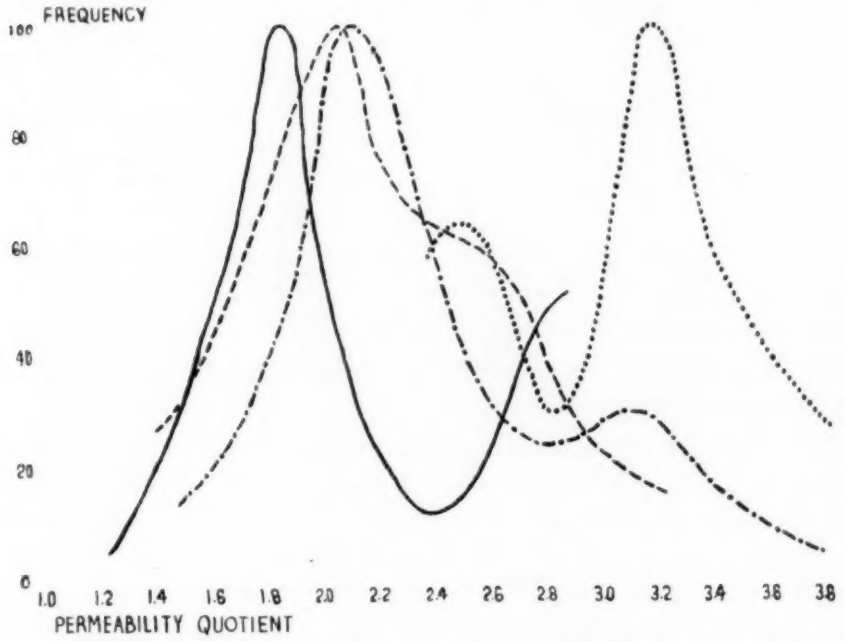

Fig. 2.—Frequency curves showing the probable distribution of permeability quotients for the various groups if a large number of cases were examined. The solid line indicates the curve for patients with active neurosyphilis; the broken line, the curve for normal infants; the line of dots and dashes, the curve for patients with treated neurosyphilis, and the lines of dots, the curve for normal adults. The results suggest that the differences are statistically significant. The height of the curve was chosen arbitrarily. This graph is presented through the courtesy of Dr. S. G. Bauer, Cambridge, England, now with the Canadian National Research Council.

per kilogram of body weight, three times a day for five days. Later investigators increased the dose to 0.04 Gm. per kilogram of body weight; this dose was used for the adults in our series. On the sixth day the bromide concentrations of the blood and the spinal fluid are determined. The ratio of bromide in the blood

3. Walter, F. K.: Die Blut-Liquorschranke, Leipzig, Georg Thieme, 1929.

to that in the cerebrospinal fluid is called the bromide permeability quotient. Walter found that the normal range of permeability quotients was from 2.90 to 3.50: these values, with slight variation, have been corroborated by other authors. The permeability quotient for neurosyphilis was found to be significantly lower, and Katzenelbogen [2] presented tabulated values to this effect, in which he compared the results of various authors.

The bromide content of the blood should be higher than 30 mg. per hundred cubic centimeters to insure an accurate determination, and cases in which the concentration was lower were not included in our series. To achieve this concentration in the blood in infants, we found it necessary to increase the single dose of sodium bromide to 0.2 Gm. per kilogram of body weight, an amount which is five times that for adults but still well below the toxic dose.

In order to adopt the colorimetric method of Walter for the estimation of bromides to the photoelectric colorimeter, it was necessary to change the dilutions of the standards and of the blood.

Standard Curve.—A calibration curve was made with known amounts of bromide. Thus, 143 mg. of sodium bromide is dissolved in distilled water, and the solution is made up to a volume of 100 cc. Standards containing 0.5, 0.75, 1, 1.5 and 2.55 cc. of the stock solution, equivalent, respectively, to 0.55, 0.83, 1.11, 1.66 and 2.77 mg. of bromine, are made up to a volume of 12 cc. with a 3 per cent solution of trichloroacetic acid. To each of these standards is added 2.4 cc. of a 0.5 per cent solution of gold chloride (Merck's acid brown), and readings are made on the Evelyn colorimeter, using filter 520. Within this range of concentrations a rectilineal curve is obtained, and a K_2 value, according to Beer's law, of 0.1245 ± 0.03 is determined.

Procedure for Blood Serum.—First, 3 cc. of serum is diluted with 9 cc. of distilled water. For each cubic centimeter of diluted serum 0.2 cc. of a 20 per cent solution of trichloroacetic acid is added. Precipitation is allowed to take place, and the solution is filtered at the end of thirty minutes. To 6 cc. of the filtrate 6 cc. of a 3 per cent solution of trichloroacetic acid and 2.4 cc. of a 0.5 per cent solution of gold chloride are added. The solution is then read in the photoelectric colorimeter with filter 520.

The results may be read off the calibration curve, or a K_2 value based on the calibration curve may be determined for each colorimeter. If the concentration of sodium bromide in serum exceeds 125 mg. per hundred cubic centimeters, the final solution should be diluted with distilled water.

It was not found necessary to allow for adsorption of bromide in the precipitated protein, as Diethelm [4] suggested. With the method described, the following recoveries of sodium bromide added to serum were obtained:

Serum Bromide,* Mg./100 Cc.	Calculated Recovery of Bromide, Mg./100 Cc.	Percentage of Recovery
92.5	92.9	99.6
44.4	46.6	95.3
95.5	92.9	102.8
34.6	33.7	102.7
93.4	92.9	100.5
54.9	55.9	98.2
95.0	89.2	106.5
64.7	67.0	96.5

* It was assumed that normal serum contained 0.4 mg. of sodium bromide per hundred cubic centimeters.

4. Diethelm, O.: On Bromide Intoxication, J. Nerv. & Ment. Dis. **71**:151 (Feb.) 1930.

Procedure for Cerebrospinal Fluid.—To 4 cc. of cerebrospinal fluid 4 cc. of distilled water and 1.6 cc. of a 20 per cent solution of trichloroacetic acid are added. The solution is allowed to stand for thirty minutes and then filtered. To 6 cc. of the filtrate 6 cc. of a 3 per cent solution of trichloroacetic acid is added, and the solution is read in the colorimeter as previously described. The result obtained with this dilution must be divided by 2, since the concentration of cerebrospinal fluid in the filtrate is twice that of the serum. The cerebrospinal fluid is not diluted so much as the serum, because the bromide concentration of the cerebrospinal fluid is usually much lower than that of the serum and a galvanometric reading above 80 is thus avoided.

Clinical Material.—The following groups of patients were tested: (1) adults showing no involvement of the central nervous system, referred to as "normal adults"; (2) adults with untreated neurosyphilis, referred to as patients with

TABLE 1.—*Barrier Permeability in 14 Adults Without Clinical or Laboratory Evidence of Neurosyphilis*

Sex	Age	Diagnosis	Cerebrospinal Fluid Protein, Mg. per 100 Cc.	Blood Bromide, Mg. per 100 Cc.	Cerebrospinal Fluid Bromide, Mg. per 100 Cc.	Bromide Permeability Quotient
F	32	Syphilis, latent, late	44.6	86.2	40.6	2.12
F	24	Syphilis, latent, early	58.8	80.5	36.7	2.19
F	20	Syphilis, latent, late	36.4	114.7	50.0	2.29
M	30	Syphilis, latent, early	30.9	68.0	26.2	2.60
F	25	Syphilis, latent, late	47.4	47.9	18.4	2.60
F	47	Syphilis, latent, late	28.4	48.2	18.4	2.62
F	31	Syphilis, secondary, treated	31.9	44.0	14.0	3.14
F	42	Syphilis, latent, late	33.8	128.0	40.6	3.15
F	41	Syphilis, latent, early	26.3	83.3	26.3	3.17
M	55	Eczema	40.0	53.3	16.6	3.21
F	40	Syphilis, latent, late	61.0	75.0	23.0	3.26
F	36	Syphilis, latent, late	58.4	61.0	17.0	3.59
F	32	Syphilis, congenital, inactive	36.4	36.5	9.7	3.76
F	21	Syphilis, latent, early	38.5	122.0	31.0	3.94
Average values			40.9			2.97*

* The average permeability quotient found in this group, 2.97, is well within the limits of values described as normal.

"active neurosyphilis"; (3) adults with neurosyphilis who have received at least one year of treatment, fever therapy and/or treatment with pentavalent arsenicals, referred to as persons with "inactive neurosyphilis," and (4) infants less than 18 months of age who were nonsyphilitic, referred to as "normal infants."

COMMENT

Our observations on increased permeability of the barrier between the blood and the spinal fluid in infants may explain the positive Wassermann reaction of the spinal fluid of infants with congenital syphilis who otherwise show no signs of neurosyphilis; this increased

TABLE 2.—*Barrier Permeability in 9 Adults with Active Neurosyphilis*

Sex	Age	Type of Neurosyphilis	Cerebrospinal Fluid Wassermann Reaction					Colloidal Gold Curve	Cell Count	Pandy Reaction	Cerebrospinal Fluid Protein, Mg. per 100 Cc.	Blood Bromide, Mg. per 100 Cc.	Cerebrospinal Fluid Bromide, Mg. per 100 Cc.	Bromide Permeability Quotient
			1 Cc.	0.6 Cc.	0.4 Cc.	0.2 Cc.	0.1 Cc.							
M	62	Asymptomatic, group 3.....	+	+	+	+	±	5555532100	200	+	109.2	97.2	89.0	1.09
M	59	Tabes dorsalis.....	+	+	+	+	+	5555532100	8	0	69.2	65.5	36.7	1.78
M	54	Asymptomatic, group 3.....	+	+	+	+	+	5555552100	..	..	97.2	62.8	34.6	1.82
M	58	Asymptomatic, group 3.....	+	+	+	..	0	1½ 1½ 2 3½ 3 2 ½ 0 0 0	2	0	72.4	101.0	55.2	1.83
F	32	Dementia paralytica.....	+	+	+	+	+	4½ 5 4 3 3 1½ 0 0 0 0	5	0	39.3	58.6	31.2	1.88
M	44	Asymptomatic, group 2.....	+	..	±	0	0	½ 1½ 1½ 2 2½ 1½ ½ 0 0 0	2	0	83.4	101.0	47.8	2.11
F	53	Asymptomatic, group 3.....	+	+	+	+	+	5 5 5 4½ 3 2 1 ½ 0 0	2	+	86.8	42.9	20.3	2.11
F	39	Asymptomatic, group 1.....	±	0	0	0	0	Normal	4	0	83.4	60.8	22.3	2.73
M	29	Asymptomatic, group 2.....	+	+	±	0	0	1½ 4 3 3 1 0 0 0 0 0	0	0	....	52.0	18.0	2.89
Average values.....											80.1			2.03*

* The average permeability quotient found in this group is in agreement with the values of various authors for patients with untreated neurosyphilis.

permeability of the barrier may permit the passage of reagin from blood into the spinal fluid.

Increased penetration of arsenicals into the spinal fluid may explain the unusually quick serologic reversal and the clinical cure of the active neurosyphilis in infants under routine therapy.

Increased permeability of the barrier in infants may be a phenomenon meriting further studies, especially with regard to therapy with penicillin.

TABLE 3.—*Barrier Permeability in 22 Nonsyphilitic Infants*

Sex	Age	Diagnosis	Blood Bromide, Mg. per 100 Cc.	Cerebrospinal Fluid Bromide, Mg. per 100 Cc.	Bromide Permeability Quotient
M	17 mo.	Pneumonia; anemia	44.4	36.7	1.21
F	18 mo.	Pneumonia, anemia	150.0	113.0	1.33
M	3 wk.	Intoxication	97.4	66.0	1.48
M	3 mo.	Pneumonia, convalescent	165.0	88.9	1.74
F	5 wk.	Infection of upper respiratory tract	196.0	110.5	1.77
M	4 mo.	Rickets; congenital heart disease; otitis media	125.0	69.8	1.79
M	4 mo.	Infection of upper respiratory tract	84.0	42.9	1.96
M	12 mo.	Lobar pneumonia	154.5	78.2	1.98
F	13 mo.	Infection of upper respiratory tract	100.2	50.4	1.99
F	13 mo.	Pneumonia, convalescent	72.3	36.1	2.00
M	3 mo.	Pneumonia, convalescent	83.6	41.5	2.01
M	3½ mo.	Pneumonia; otitis media	120.0	55.6	2.16
F	2 mo.	No disease	97.1	44.6	2.18
F	23 mo.	Pneumonia, convalescent	85.2	36.4	2.34
F	4 mo.	Otitis media	50.5	20.7	2.44
M	14 mo.	Nutritional anemia	75.1	30.4	2.47
M	5½ mo.	Eczema	86.2	32.4	2.66
F	4 mo.	Otitis media	66.0	24.4	2.70
M	15 mo.	Nutritional anemia; infection of upper respiratory tract	87.0	30.4	2.86
F	5 mo.	Otitis media	31.9	11.1	2.87
M	3 mo.	Tracheobronchitis, convalescent	49.4	15.2	3.25
M	5 wk.	Infection of upper respiratory tract	36.6	10.8	3.39
		Average value			2.21*

* The average permeability quotient for this group of normal infants is significantly lower than the values listed for adults and closely approaches the figures found for adults with neurosyphilis.

SUMMARY

The permeability of the blood–spinal fluid barrier was determined for nonsyphilitic infants and was compared with that for normal adults and for adults with neurosyphilis. The values for infants were significantly lower than those for adults and were comparable to the values for adults with neurosyphilis.

Walter's bromide method was used for this investigation, and adaptation of this method to photoelectric readings is described.

TABLE 4.—*Barrier Permeability in 31 Adults with Well Treated and Inactive Neurosyphilis*

Sex	Age	Type of Neurosyphilis	Cerebrospinal Fluid Wassermann Reaction					Colloidal Gold Curve	Cell Count	Pandy Reaction	Cerebrospinal Fluid Protein, Mg. per 100 Cc.	Blood Bromide, Mg. per 100 Cc.	Cerebrospinal Fluid Bromide, Mg. per 100 Cc.	Bromide, Permeability Quotient
			1 Cc.	0.6 Cc.	0.4 Cc.	0.2 Cc.	0.1 Cc.							
M	52	Diffuse vascular with epilepsy	+	+	±	..	0	0 ½ 1 2 2 1 ½ 0 0 0	2	0	80.4	47.6	33.5	1.42
M	58	Meningovascular	+	+	+	+	+	1 1 1½ 1½ 2 1½ ½ 0 0 0	2	0	107.6	114.7	71.1	1.61
M	46	Asymptomatic, group 1	0	0	0	0	0	Normal	0	0	42.0	46.0	26.5	1.73
F	52	Meningovascular	+	+	±	0	0	Normal	0	0	80.2	90.7	47.8	1.90
M	59	Meningovascular	+	±	..	..	..	0 ½ 1 2 1 0 0 0 0 0	—	—	100.6	30.0	15.5	1.94
F	48	Meningovascular	+	±	0	0	0	Normal	0	0	36.4	56.2	28.9	1.94
M	46	Meningovascular	+	+	+	+	±	½ 1 1½ 2 1 0 0 0 0 0	3	0	74.0	59.6	30.5	1.95
M	48	Meningovascular	+	+	±	0	0	Normal	1	0	56.4	60.0	30.0	2.00
F	42	Dementia paralytica	+	+	+	±	0	1½ 1½ 2 2 1 0 0 0 0 0	2	0	75.6	123.0	59.8	2.06
M	58	Tabes dorsalis	0	0	0	0	0	Normal	0	0	78.8	125.5	59.6	2.11
M	49	Dementia paralytica	+	+	+	+	±	Normal	2	0	38.6	53.5	25.2	2.12
F	59	Tabetic dementia paralytica	+	+	+	+	+	2½ 4 4 4½ 3 1½ ½ 0 0 0	5	0	....	66.4	31,2	2.13
M	48	Meningovascular	+	+	+	+	+	1 1½ 2 2 1½ ½ 0 0 0 0	2	0	38.7	37.5	17.5	2.14
F	37	Asymptomatic, group 2	+	..	..	..	..	Normal	0	0	40.0	62.5	27.7	2.26
M	44	Meningovascular	+	+	+	±	0	Normal	1	0	64.6	68.4	30.3	2.26
M	58	Asymptomatic, group 1	±	0	0	0	0	Normal	0	0	67.6	80.5	35.6	2.26
M	41	Meningovascular	+	+	+	+	+	5 5 4½ 3 2 1 0 0 0 0	0	0	21.6	62.5	27.7	2.26
M	67	Tabes dorsalis	+	±	±	0	0	Normal	0	0	63.2	84.9	36.7	2.31
F	35	Meningovascular with epilepsy	+	+	+	+	+	½ 2 3 2 1 ½ 0 0 0 0	0	0	48.0	48.0	20.4	2.35
M	38	Dementia paralytica	+	+	+	+	+	5 5 5 5 5 5 4 1½ 1 0	6	0	83.4	55.2	22.3	2.48
M	43	Tabes dorsalis	+	+	±	0	0	1½ 1½ 1½ 3½ 3 2 1½ 0 0 0	2	0	61.8	91.0	36.1	2.52
M	49	Asymptomatic, group 2	±	0	0	0	0	Normal	0	0	74.0	100.0	38.9	2.57
F	27	Asymptomatic, group 3	+	+	+	..	±	1 1½ 2 ½ ½ 0 0 0 0 0	2	0	70.8	52.6	18.4	2.86
M	49	Meningovascular	+	+	+	..	±	1½ 1½ 2 3 2½ 1 0 0 0 0	2	0	47.4	53.6	18.0	2.94
F	22	Asymptomatic, group 1, early	0	0	0	0	0	Normal	0	0	31.5	112.0	38.0	2.95
M	31	Meningovascular	+	+	±	..	..	2½ 2½ 3 2 1½ 1 0 0 0 0	2	0	71.2	73.8	24.6	3.00
M	41	Meningovascular	+	+	+	±	0	1 1½ 2 1½ 1 ½ 0 0 0 0	0	0	54.1	54.0	17.0	3.18
F	42	Asymptomatic, group 3	+	+	+	+	+	0 ½ 1 1½ 2 1 ½ 0 0 0	0	0	53.0	60.6	18.4	3.29
F	27	Asymptomatic, group 1	0	0	0	0	0	Normal	2	0	58.4	165.0	50.0	3.30
M	43	Dementia paralytica and optic nerve atrophy	+	+	+	+	+	1½ 1½ 4½ 4 2½ 1½ ½ 0 0 0	2	+	49.5	50.0	12.0	4.17
F	40	Asymptomatic, group 3	+	+	+	+	+	1 1½ 3 2½ 2 0 0 0 0 0	0	0	51.9	125.0	30.0	4.17
		Average values									60.7*			2.46*

* The average permeability quotient and the total protein values for this group lie between the figures listed for adults and active neurosyphilis and for normal adults.

These observations explain positive Wassermann reactions of the spinal fluid of syphilitic infants who otherwise show no evidence of neurosyphilis, clinically or with laboratory tests.

It is suggested that positive Wassermann reactions of the cerebrospinal fluid of syphilitic infants should not be considered proof of neurosyphilis in the absence of other evidence.

Miss Barbara Dean, Department of Dermatology, Royal Victoria Hospital, prepared the tables.

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USE OF QUANTITATIVE PARASITE INOCULATION DOSES IN PLASMODIUM VIVAX MALARIA THERAPY

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CUMULATIVE experience with therapeutic malaria in the management of neurosyphilis during the past twenty-five years has resulted in refinement of technics and in a clearer understanding of the characteristics of induced malarial infection. The febrile course of Plasmodium vivax malaria, following either natural or artificial inoculation, in most instances does not display the regular tertian paroxysms commonly described in textbooks. The majority of infections exhibit quotidian cycles with varying degrees of irregularity. At the onset of clinical activity, following mosquito inoculation or the usual administration of a 5 to 10 cc. inoculum of blood at institutions utilizing therapeutic malaria, a period of several days of remittent fever, characterized by continuous low grade elevations of temperature, to 101 or 103 F., is experienced. This period of remittent fever is commonly accompanied with severe malaise and exhaustion, often debilitating the patient prior to the establishment of true malarial paroxysms. Since the accepted criterion for determining the therapeutically effective amount and duration of fever therapy of neurosyphilis consists either in the number of paroxysms reaching 104 F. or more or in the number of hours of fever experienced at a temperature above 103.6 F., the period of remittent fever, exhausting the patient before clinical activity is regulated, contributes little to the therapeutic course.

Investigators in malaria research consider this initial period of remittent fever the result of asynchronization of different broods of malaria parasites. This asynchronization of parasites following intravenous inoculation is apparently produced by the injection of a large number of organisms in different stages of schizogony, resulting in remittent fever when clinical levels of parasitemia are reached. Synchronization of these broods occurs only after several days of clinical activity has permitted domination by a single brood and cycle.

It was the purpose of the investigation here reported to control the technics of inoculation in order to eliminate the disturbing period of remittent fever and to have as many patients as possible experience paroxysms of therapeutic benefit at the onset of clinical activity. It seemed logical that if a single parasite were injected into a recipient's blood stream, only one brood of parasites would mature and only one cycle of paroxysms, typically tertian, would eventuate. The inoculation of single trophozoites is now being accomplished with some degree of success at the Station for Malaria Research (Rockefeller Foundation), Tallahassee, Fla., with use of the micropipet. Such a technic requires the utmost skill, is time consuming and must be confined to research laboratories.

The quantitative parasite count, performed by a relatively simple method, has initiated a technic of inoculation based on predetermined parasite doses low enough to eliminate or suppress the period of remittent fever. Total doses of less than 500,000 parasites often require laborious dilution methods, which appreciably diminish the clinical applicability of the technic. For that reason, doses ranging from 1,000,000 to 150,000,000 parasites were used in this study. In many instances intradermal inoculation was attempted with the thought that few parasites would reach the blood stream, resulting in less asynchronization and greater regularity of the febrile response. The results of a comparative study of the duration of the period of remittent fever and the type of febrile cycle produced by the inoculation of P. vivax parasites intradermally; intravenously, in varying parasite doses, and by mosquito application are reported in this communication.

MATERIAL AND METHOD

From June 25, 1944 to Aug. 31, 1945, a total of 265 patients with neurosyphilis were inoculated with P. vivax. Thirty-six patients experiencing spontaneous remissions prior to the completion of a therapeutic course and requiring a course of quartan malaria therapy, or inoculation with Plasmodium falciparum, were excluded from this study because of their immune responses. Of the remaining 229 white patients, the results for a series of 205 were actually analyzed. The 24 patients for whom results were omitted from the analysis were those who had a definite history of previous attacks of natural malaria. This omission was justified by the observation that the period of remittent fever and the type of the paroxysmal cycle were dependent not only on the technic of inoculation but on the degree of immunity to malaria of the individual patient. A previous study of homologous and heterologous immunity to P. vivax malaria with the cross inoculation method[1] clearly indicated that the ability of a partially immunized patient to deal with injected parasites is quite different from that of a susceptible patient.

1. Kaplan, L. I.; Read, H. S., and Becker, F. T.: Homologous and Heterologous Strains of Plasmodium Vivax: A Cross-Inoculation Study of Malaria Strain Immunity, J. Lab. & Clin. Med. **31**:400, 1946.

Technics of Inoculation.—1. Mosquito Inoculation: Three to 6 mosquitoes from lots [2] of known infectivity were applied (in individual cages) to the upper extremity and axilla of 58 patients. After application, each mosquito was dissected in order to determine the approximate degree of infectivity from the density of sporozoites extruded from the salivary glands. In all instances a minimum of 2 infected mosquitoes per patient was considered necessary for a successful clinical "take."

2. Intradermal Inoculation: Ordinary tuberculin syringes were used to inject whole blood directly from a donor into 4 wheals on the recipient's forearms (0.05 cc. of blood in each wheal). Donors with parasite counts of approximately 5,000 per cubic millimeter were employed in most instances in order to give a total dose of approximately 1,000,000 to 2,000,000 parasites in the 0.2 cc. of intracutaneously injected blood. Twenty-six of 34 patients inoculated with this technic completed therapeutic courses, and their data were included in the analysis.

3. Intravenous Inoculation: The single syringe technic, with which whole blood is directly transferred from donor to recipient without the use of anticoagulants, was employed. Inoculums varied from 0.05 to 10 cc., depending on the quantitative parasite count of the donor. Total doses injected with this method ranged from 1,000,000 to 150,000,000 parasites. Fifty-six patients received doses of 1,000,000 to 5,000,000 parasites; 29 received 6,000,000 to 25,000,000 parasites, and 36 received 26,000,000 to 150,000,000 parasites. An illustration is given.

Quantitative parasite count of donor, 5,000 per cubic millimeter
Inoculum of 1 cc., 5,000,000 parasites
Inoculum of 0.2 cc., 1,000,000 parasites
Inoculum of 10 cc., 50,000,000 parasites

The Quantitative Parasite Count.—The technic of the quantitative parasite count, Boyd's modification of that described by Earle and Perez,[3] may be described as follows:

1. Materials Required

(*a*) Capillary pipets graduated to deliver 5 cu. mm. of blood.

(*b*) Glass slides on which are ruled or etched rectangles measuring 3 by 15 mm.

(*c*) Microscope, the ocular of which contains a Howard disk micrometer. The surface of the micrometer is ruled with one large square, divided into 16 minor squares and so calibrated that with a predetermined tube length the area on a slide covered by the large square on the micrometer is known.

(*d*) Diluted Giemsa stain.

2. Method

(*a*) Exactly 5 cu. mm. of blood is discharged onto the ruled rectangle of the slide, care being taken to avoid bubbles. With a needle point the blood is carefully spread out to the edges and into the corners of the ruled area. The film is allowed to stand in a horizontal position until dry. Since 5 cu. mm. of blood is spread out over 45 sq. mm., there will be spread over each square millimeter of the rectangle 0.11, or 1/9, cu. mm. of blood.

(*b*) The smear is stained with Giemsa's stain, as is any other thick smear, and washed, drained and dried.

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2. Supplied by Dr. Boyd.

3. Earle, W. C., and Perez, M.: Enumeration of Parasites in the Blood of Malarial Patients, J. Lab. & Clin. Med. **17**:1124, 1932.

(*c*) Assuming that the micrometer disk has been calibrated so that the large square covers an area of 0.01 sq. mm. on the slide, it will be necessary to count the parasites on the stained smear in 100 consecutive and discrete fields to estimate the parasites in the blood spread over 1 sq. mm. The fields should be selected as the smear is traversed on different parallel lines. The total of the parasites counted in 100 fields will, when multiplied by 9, give the number per cubic millimeter (fig. 1).

Tabulation of Data.—This investigation was concerned chiefly with the influence of methods of inoculation on the duration and severity of the period of remittent fever at the onset of clinical malaria. Continuous days of remittent fever were

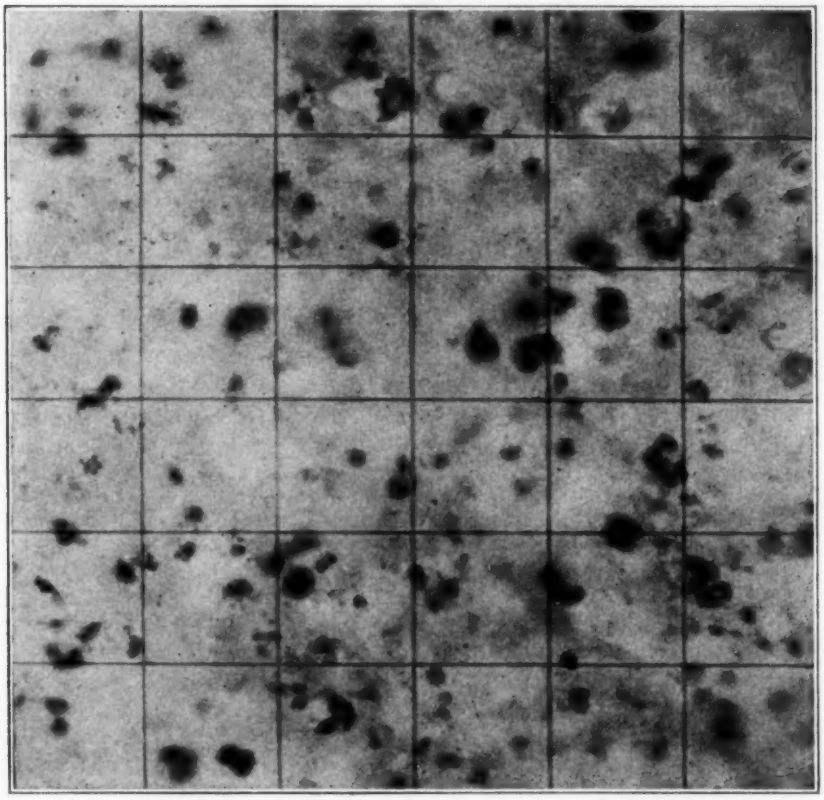

Fig. 1.—Microscopic field (95 magnification objective), showing parasites in a thick smear seen through the Howard disk.

calculated from the time of the initial elevation of temperature above 100 F. to the first normal temperature record prior to the onset of effective paroxysms. During this period no decrease in temperature below 100 F. occurred. The first twenty-four hours of the period of remittent fever was excluded from the calculation in order to make it possible to tabulate no days of remittent fever for those patients initiating activity with an immediate paroxysmal cycle. Examples of febrile courses with different periods of remittent fever are illustrated in figure 2.

Though variation in the technic of the inoculation did not have as significant an effect on the subsequent cycle of paroxysms as it did on the period of remittent

fever, the percentage of patients in each inoculation group exhibiting tertian paroxysms was, nevertheless, recorded. The known influence of the donor's cycle (quotidian or tertian) in predetermining the subsequent cycle in the recipient was in large part canceled by an approximately equal distribution of donors' cycles (24 to 26 per cent tertian) in each group.

Because of the regularity with which the prepatent and incubation periods are related to the parasite dose, varying inversely with the total dose administered intravenously, in such a series of susceptible patients, the duration of these periods was not recorded in this study.

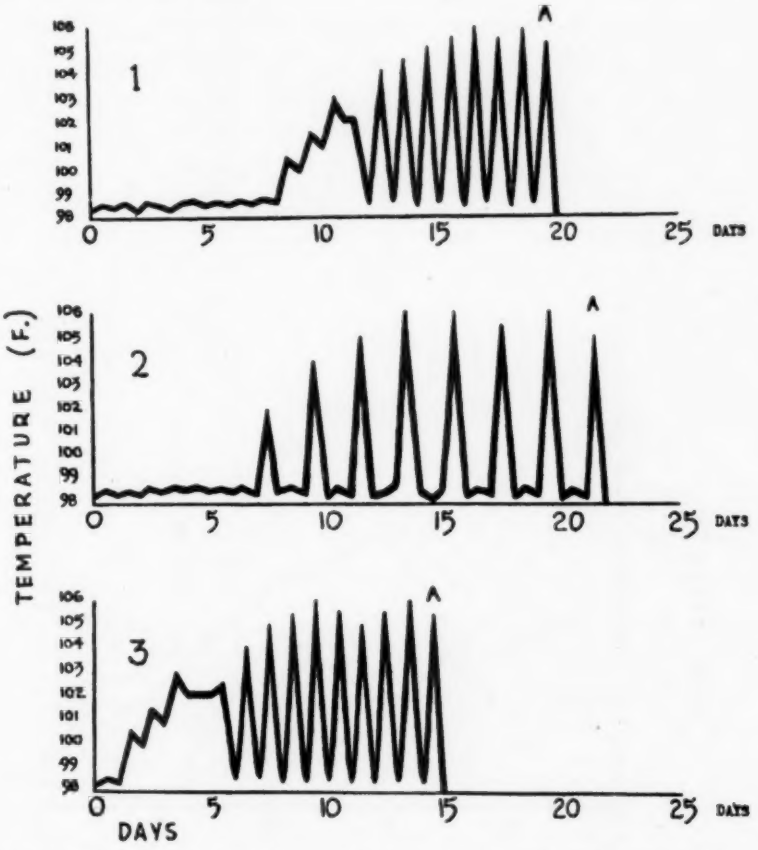

Fig. 2.—Febrile courses with various periods of remittent fever. Each temperature graph starts with the day of inoculation. *A*, at the end of each course, signifies the institution of quinacrine therapy. *1* shows the febrile course following mosquito inoculation (three days of remittent fever); *2*, the course following intradermal inoculation (no days of remittent fever), and *3*, the course following intravenous inoculation with 100,000,000 parasites (five days of remittent fever).

RESULTS

The data summarized in the table indicate the number of patients inoculated with each technic, the type of subsequent febrile cycles and the percentage of patients, by groups, experiencing periods of remittent

fever lasting no, one, two, three, four or five days. Figures 3 and 4 show the distribution curves for these figures. Intradermal inoculation eliminated the period of remittent fever in 42.3 per cent of the patients and resulted in periods of remittent fever lasting two days or less in 78.9 per cent. This result, as compared with the results of mosquito inoculation (8.6 per cent of patients with a period of no days of remittent fever and 37.9 per cent with two days or less of remittent fever) and

Summary of Data

Method of Inoculation *	No. of Patients Inoculated	Percentage with Tertian Cycles	Distribution of Patients (%) by Period (Days) of Remittent Fever					
			0	1	2	3	4	5
Intradermal	26	57.8	42.3	23.1	11.5	19.3	0.0	3.8
Mosquito	58	22.4	8.6	17.2	12.1	32.8	15.5	13.8
Intravenous (1-5 M)	56	37.5	23.2	17.8	17.8	17.8	16.2	7.2
Intravenous (6-25 M)	29	31.0	13.8	10.3	31.0	24.1	13.8	7.0
Intravenous (26-150 M)	36	25.0	11.1	11.1	22.2	13.9	19.5	22.2
Intravenous (1 M)	28	42.9	35.7	17.9	14.3	14.3	14.3	3.5
Intravenous (2-5 M)	28	32.1	10.7	17.9	21.4	21.4	17.9	10.7

* M stands for millions, e. g., 1,000,000-5,000,000.

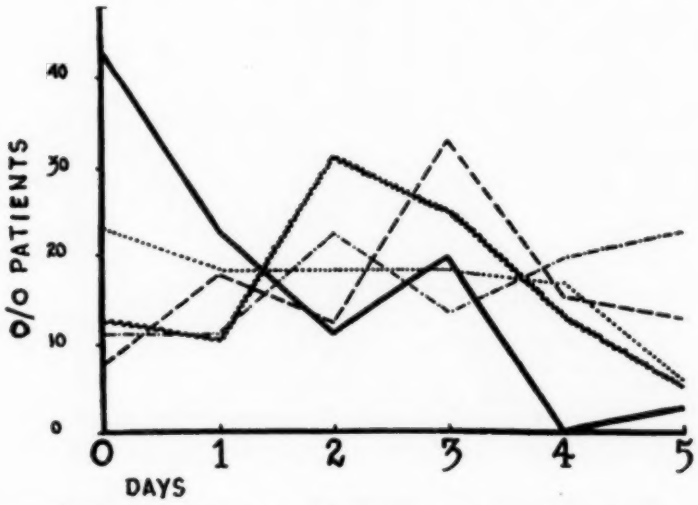

Fig. 3.—Distribution curves for the duration of remittent fever with each method of inoculation. The best results are indicated by the highest percentage of patients experiencing no, one or two days of remittent fever.

In this figure, the solid line represents intradermal inoculation; the line of dashes, mosquito inoculation; the line of dots, intravenous inoculation with 1,000,000 to 5,000,000 parasites; the wavy line, intravenous inoculation with 6,000,000 to 25,000,000 parasites, and the line of dots and dashes; intravenous inoculation with 26,000,000 to 150,000,000 parasites.

with those of intravenous inoculation of 26,000,000 to 150,000,000 parasites (11.1 per cent of patients with no days of remittent fever and 44.4 per cent with remittent fever lasting two days or less), demon-

strates that the severity of the initial clinical activity in P. vivax malaria is significantly diminished by the employment of intradermal inoculation. However, of 34 patients originally inoculated with this method, 6 failed to exhibit clinical activity, although they demonstrated clinical responses characteristic of susceptible patients on subsequent intravenous reinoculation with the same strain of P. vivax. This indicated a serious technical failure, resulting probably from the unpredictable destruction of parasites before they reached the circulation. Therefore, although intradermal inoculation most satisfactorily diminishes the period of remittent fever, it cannot be recommended as a routine procedure because of the high incidence (18.8 per cent) of unsuccessful "takes" in susceptible patients. For this reason, closer attention was directed to the intravenous method of inoculation with total doses of less than 5,000,000 parasites.

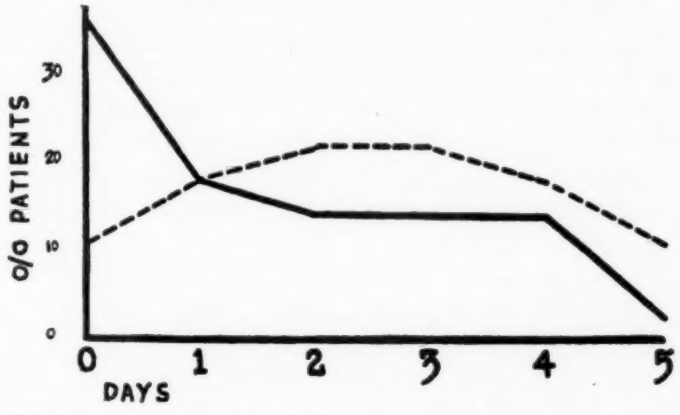

Fig. 4.—Distribution curves for the duration of remittent fever with intravenous inoculation of low parasite doses. The continuous line, closely simulating the curve for intradermal inoculation (fig. 3), represents the results with the recommended dose of 1,000,000 parasites.

In this figure, the solid line represents intravenous inoculation with 1,000,000 parasites, and the broken line, intravenous inoculation with 2,000,000 to 5,000,000 parasites.

Mosquito inoculation, resulting in remittent fever lasting three days or longer in a high percentage of cases (62.1 per cent), has other disadvantages which limit its usefulness to hospitals and laboratories especially equipped for such procedure. The necessity for maintenance of an insectary and of technicians trained in mosquito dissection and application prohibits the adoption of this technic in many institutions intimately concerned with the treatment of neurosyphilis. The increased incidence of malaria relapses following the mosquito-induced disease as compared with the incidence following other methods of inoculation detracts further from its practicability.

Intravenous inoculations with comparatively small parasite doses (1,000,000 to 5,000,000) were followed by periods of remittent fever more severe than the periods of fever after intradermal inoculation and less severe than those following mosquito application and intravenous inoculation with heavy parasite doses (26,000,000 to 150,000,000). The period of remittent fever was absent in 23.2 per cent and lasted two days or less in 58.8 per cent of patients in this group. However, a further breakdown of this inoculation series into a group receiving inoculums of 1,000,000 parasites and another receiving 2,000,000 to 5,000,000 parasites elucidates the effect produced by progressive decrease in the parasite dose. The patients inoculated intravenously with 1,000,000 parasites exhibited a distribution curve most closely resembling the curve for intradermal inoculation, with 35.7 per cent having absence of remittent fever and 67.9 per cent experiencing two days or less (fig. 4). These observations lead one to suspect that further decrease in the intravenous parasite dose, e. g., to 100,000 parasites or less, would shorten or eliminate the period of remittent fever in a still greater percentage of patients. However, the difficulties encountered in injecting doses of less than 1,000,000 parasites intravenously, such as dilution methods, and the greater risk of technical failure seem to justify the adoption of intravenous administration of the 1,000,000 parasite dose as the most practicable method of shortening the initial, exhausting period of remittent fever of induced malaria.

Although experience with therapeutic malaria has demonstrated that the recipient's febrile cycle depends to some extent on the donor's previous cycle, an interesting result of varying the technic of inoculation was observed in this study. Tertian cycles were exhibited by 24 to 26 per cent of donors in each blood inoculation group. In spite of this relatively equal cycle distribution among donors, tertian paroxysms were experienced in the largest number of patients (57.8 per cent) in the intradermal inoculation group and in the smallest number of patients (25 per cent) in the intravenously inoculated group (26,000,000 to 150,000,000 parasites). The percentage of patients with tertian cycles following intravenous inoculation varied inversely with the parasite dose, with 42 per cent occurring in the group receiving the 1,000,000 parasite dose, 32.1 per cent in the group receiving the 2,000,000 to 5,000,000 parasite dose, 31 per cent in the group receiving the 6,000,000 to 25,000,000 parasite dose and 25 per cent in the group receiving the 26,000,000 to 150,000,000 parasite dose. These data suggest that the better tolerated tertian cycle, like the shortened period of remittent fever, is more frequently associated with intradermal inoculation and with the intravenous inoculation of 1,000,000 parasites than with the other inoculation technics.

SUMMARY AND CONCLUSIONS

Elimination of the ordinarily long period of remittent fever initiating the clinical course of therapeutic malaria prevents the early exhaustion of patients. An elaborated investigation of the relationship of technics of inoculation to this period of remittent fever has resulted in observations of clinical value.

Intradermal inoculation was followed by the shortest and least severe period of remittent fever, with 76.9 per cent of patients experiencing fever for two days or less and 42.3 per cent not at all. However, the occurrence of 18.8 per cent of unsuccessful "takes" as a result of technical difficulties makes the routine use of this method unjustified.

Intravenous inoculations with doses ranging from 1,000,000 to 150,000,000 parasites revealed in susceptible persons that the higher the parasite dose the longer was the period of remittent fever in the greater percentage of patients. The lower the parasite dose the shorter and less severe was the remittent fever, resembling the results following intradermal inoculation.

The intravenous inoculation of 1,000,000 P. vivax parasites, determined by correlating the amount of inoculum with the quantitative parasite count of the donor, is recommended as a standard procedure in the therapy of neurosyphilis when one is dealing with susceptible white patients. This technic eliminated the period of remittent fever in 35.7 per cent of patients and shortened it to two days or less in 67.9 per cent of patients in this study. Similarly, if the paroxysmal cycle of the donor is disregarded, the greatest percentage of tertian cycles after intravenous inoculation will follow the employment of this parasite dose.

Mrs. Winifred Eickstaedt, Sgt. Ivan G. Strickler and Cpl. Richard P. Roy gave secretarial, laboratory and statistical aid in the preparation of this paper.

RESISTANCE TO INSULIN IN MENTALLY DISTURBED SOLDIERS

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PREVIOUS investigators[1] have noted abnormalities in the carbohydrate metabolism of psychotic persons. Their studies have concentrated chiefly on the response of the blood sugar to ingested dextrose, and have revealed that there exists a reduction in the dextrose tolerance, with resulting diabetic-like levels of blood sugar. To determine whether this abnormal trend is due to a dysfunction of the insulinogenic mechanisms, Freeman[1a] and Braceland[1c] investigated the insulin tolerance of schizophrenic subjects and found that such patients show a less pronounced fall in blood sugar after the administration of insulin than do normal subjects.

In order to determine whether resistance to insulin is a characteristic feature of the schizophrenic psychosis alone, I made a study of this function in other mental disorders.

METHOD AND MATERIAL

The subjects included 93 soldiers discharged from the Army for psychiatric disorders. The average age of the patients lay between 20 and 25. Their nutrition was on the whole good, the average nutritional index being 98 per cent of the ideal (according to standards of the Metropolitan Insurance Company). Few were grossly overweight or underweight. The average stay in the Army before psychiatric symptoms appeared was six months. Each patient had been confined in a mental disease hospital in the military service for an average of two months before the present study. These patients showed many varieties of psychiatric symptoms, although in general the clinical status showed less clearly defined and more transitory types of disturbance than are ordinarily found in the civilian population.

The technic of the test was simple. After a postabsorptive period of at least fourteen hours, a control sample of blood was taken, and insulin was then administered intravenously in a dose of 0.1 unit per kilogram of body weight. Subsequent samples of blood were taken at regular thirty minute intervals, with the patient lying quietly in bed.

From the Memorial Foundation for Neuro-Endocrine Research, and the Research Service of the Worcester State Hospital.

1. (*a*) Freeman, H.; Rodnick, E. H.; Shakow, D., and Lebeaux, T.: The Carbohydrate Tolerance of Mentally Disturbed Soldiers, Psychosom. Med. **6**:311, 1944. (*b*) Robinson, G. W., Jr., and Shelton, P.: Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves in Nervous and Mental Patients, J. A. M. A. **114**:2279 (June 8) 1940. (*c*) Braceland, F. J.; Meduna, L. J., and Vaichulis, J. A.: Delayed Action of Insulin in Schizophrenia, Am. J. Psychiat. **102**:108, 1945.

From the first 29 subjects tested by us the blood was withdrawn over a total period of two hours, according to the technic of Fraser, Albright and Smith.[2] Since the reaction in the second hour showed no abnormality, it was decided to restrict the study to the first hour in the rest of the series. The blood was analyzed for sugar by the Folin-Wu method (macroalkaline tartrate), with the actual reading made with the use of a photoelectric colorimeter.

RESULTS

The results of the tests on the patients were compared with our own values for a series of 20 normal men (table 1). When the whole group of patients (93) is considered, it may be seen that during the course of the first hour the chief difference between the mentally disturbed patients and the normal group lay in the mean value for the thirty minute period. For the patients it was 41.4 mg. per hundred cubic centimeters, as compared with 29.6 mg. for the normal subjects. The difference of 11.8 mg. between the mean level of the blood sugar for the patients and that for the normal subjects is statistically

TABLE 1.—*Means of Values for Blood Sugar During the Insulin Tolerance Test in 20 Normal Men and 93 Mentally Disturbed Soldiers*

Type of Subject	Number	Blood Sugar, Mg. per 100 Cc.				
		Fasting Value	After Insulin			
			30 Min.	60 Min.	90 Min.	120 Min.
Normal	20	87.1	29.6	61.1	75.3	79.6
Psychiatric	93	87.1	41.4	65.3	68.2 *	78.8 *

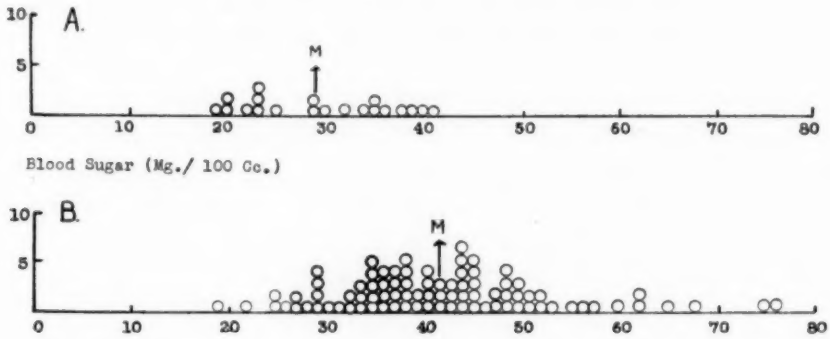
* Observations on 29 subjects.

significant, the probability of its occurring by chance being less than 1 in 100. The fasting values and those for the sixty minute period were not particularly dissimilar. This lesser degree of hypoglycemia in the patients indicates a resistance to the blood sugar—reducing effect of insulin, which is quite similar on the whole to that noted in the chronically ill schizophrenic group studied previously,[3] whose mean thirty minute level was 39.2 mg. per hundred cubic centimeters. For 29 of the present patient subjects the values for the blood sugar were followed for two hours. In these patients it was found that the level of recovery was quite similar to that found in the normal subjects, as was true for the civilian schizophrenic subjects whose illness was prolonged. In

2. Fraser, R.; Albright, F., and Smith, P. H.: The Value of the Glucose Tolerance Test, the Insulin Tolerance Test and the Glucose-Insulin-Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism, J. Clin. Endocrinol. **1**:297, 1944.

3. Freeman, H.; Looney, J. M.; Hoskins, R. G., and Dyer, C. F.: Results of Insulin and Epinephrine Tolerance Tests in Schizophrenic Patients and in Normal Subjects, Arch. Neurol. & Psychiat. **49**:195 (Feb.) 1943.

short, then, the outstanding defect in this group of patients was a failure to show a blood sugar–reducing effect; the secondary response, or rise in blood sugar, was normal.



Frequency distributions of values for blood sugar thirty minutes after the injection of insulin in 20 normal men (*A*) and 93 mentally disturbed men (*B*). *M* (mean) for the normal subjects was 29.6 ± 1.64 mg. per hundred cubic centimeters, with a standard deviation of 7.4 mg.; the mean for the psychiatric subjects was 41.4 ± 1.11 mg. per hundred cubic centimeters, with a standard deviation of 10.7 mg. per hundred cubic centimeters.

Not all patients showed this insulin-resistant effect. The chart shows the distribution of values for the blood sugar for the thirty minute period in normal and in psychiatric subjects. The values for

TABLE 2.—*Means of Blood Sugar Values at Point of Maximum Hypoglycemia (Thirty Minutes After Administration of Insulin) in 20 Normal and 93 Mentally Disturbed Men Classified According to Diagnosis Groups*

Type	Number	Blood Sugar, Mg. per 100 Cc.
Normal	20	29.6
All patients with psychoses	71	41.2
Schizophrenia	45	40.7
Manic-depressive psychosis	5	43.6
Undiagnosed type	9	41.4
Other types	12	41.8
All nonpsychotic patients	22	42.7
Psychoneurosis	12	44.6
Psychopathic personality	7	40.0
Other disturbances	3	41.3

the normal subjects are distributed within a narrow zone, between 19 and 41 mg. per hundred cubic centimeters. For the patients, the values extend over a much broader range, from 19 to 76 mg. per hundred cubic centimeters. Forty-three of the patients, or 46 per cent, had values for the blood sugar that were higher than the maximum reading

for any normal subject. This figure corresponds closely with that found in the chronic schizophrenic population (41 per cent).[3]

The patients were classified by diagnostic groups (table 2) based on the decisions of the research staff of the hospital. The majority (71) were found to be psychotic, the predominant disease being schizophrenia. Of the 22 nonpsychotic patients the larger number (12) were considered to be psychoneurotic. The lower reactivity to insulin was found to occur with approximately equal frequency in all diagnostic groups, so that there was no apparent relation to the type of mental disturbance.

Resistance to exogenous insulin is present in patients with schizophrenia [4] but is not restricted in psychotic states to that condition alone. It is a phenomenon widespread throughout all types of mental disturbance. In this sense it is similar to the frequent occurrence of decreased dextrose tolerance in persons who show various types of psychiatric abnormalities [1a, b] and is probably related to similar physiologic factors, although analysis shows no correlation between the two phenomena in individual subjects. It is of interest, also, that resistance to insulin was present in these patients, whose illness was of recent onset, to as great a degree as in the previous group of schizophrenic patients, whose average duration of illness was four years.

COMMENT

The physiologic background for this resistance to insulin is as yet not known. The main factors to be considered are the functional state of the liver and the activity of the endocrine glands. Production of insulin is probably adequate—otherwise one would expect abnormal fasting values. It may be delayed, as Braceland, Meduna and Vaichulis [1c] have shown because of the presence of anti-insulin factors. Of these factors, it does not seem likely that adrenomedullary activity is at fault because (*a*) the response to hypoglycemia (which calls forth sympathicomimetic substances) is essentially normal, and (*b*) the response of the blood sugar to injected epinephrine is less in schizophrenic patients than in normal persons.[3] Logically, therefore, one would not expect that in psychiatric subjects its anti-insulin effect would be greater.

Resistance to insulin is found in patients with clinical hyperpituitarism, hyperadrenalism and hypothyroidism.[2] Our patients [5] were characterized by low metabolic rates, a fact which, among others, suggests that the role of the thyroid may be an important one. Investigation is going on with respect to the other glands.

The effect of insulin resistance in psychiatric disturbances is as yet obscure. One cannot predicate from this investigation that the

4. Braceland and associates.[1c] Freeman and associates.[3]

5. Hoskins, R. G., and Freeman, H.: Unpublished data.

relative efficacy of endogenously produced insulin is lessened, but the assumption would be valid, both from the results of the present study and the observation of a decreased dextrose tolerance. In the final analysis, it would mean that glucose is not properly utilized, and from this point of view prolonged dysfunction may be a factor either in the activation or in the perpetuation of a mental disturbance, since the central nervous system is dependent on carbohydrate alone for its metabolic needs.

SUMMARY

A study of the sensitivity of the blood sugar response to injected insulin in a series of 20 normal men and of 93 mentally disturbed soldiers revealed that the mean maximum level of hypoglycemia (in thirty minutes) was 29.6 mg. per hundred cubic centimeters in the former and 41.4 mg. per hundred cubic centimeters in the latter. This difference in reactivity was statistically significant. Forty-six per cent of the patients showed a less pronounced drop in blood sugar than any of the normal subjects. The secondary rise in blood sugar following the hypoglycemia was the same in the two groups. This resistiveness to insulin was noted with all clinical types of mental disturbance and is probably indicative of a coincidental change in the reactivity of the endocrine factors controlling the regulation of blood sugar.

CONCLUSION

Acute episodes of mental disturbance, irrespective of diagnostic type, are characterized by resistance to the hypoglycemic effect of injected insulin.

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HISTOPATHOLOGIC CHANGES IN CEREBRAL MALARIA AND THEIR RELATION TO PSYCHOTIC SEQUELS

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WORLD War II has again conferred outstanding importance on the problem of malaria. This illness, which more than any other was responsible for casualties in World War I, has played a tremendous role in the second conflict as well (Wales [1]). The neuropsychiatric complications of malaria are more common than are generally known and have been recognized since ancient times. Malarial psychoses were known even to Hippocrates and Galen. Chavigny,[2] Porot and Gutmann,[3] Hesnard [4] and others made extensive studies of the malarial psychoses and proposed various classifications of them. Pasmanik,[5] who studied more than 5,000 cases of malaria, noted mental disorders in 2 per cent of them. Forrester,[6] who studied this problem during the first world war, stated that malaria was the main cause of insanity among the Macedonian troops. In a monograph published in 1927, Anderson [7] dealt in detail with malarial psychoses and neuroses, paying special

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Dr. Hans Meth, of Quito, Ecuador, provided the anatomic material, the clinical record and the necropsy reports of cases 1 and 2, and Dr. Erwin Klein, of Guayaquil, Ecuador, provided the material and record on case 3. These physicians regret that, on account of the limited facilities available in the district where the patients resided, the laboratory work-up could not be as thorough as was desired.

1. Wales, H. G. Q.: Malaria and War in the Pacific, Hygeia **21**:102 (Feb.) 1943.

2. Chavigny: Complications nerveuses et mentales du paludisme, Encéphale **1**:387-391, 1912.

3. Porot, A., and Gutmann, R. A.: Les psychoses du paludisme, Paris méd. **22**:518-522 (Dec. 29) 1917; **27**:241-248 (March 30) 1918.

4. Hesnard: Les psychoses palustres prolonguées, Cong. d. méd. aliénistes et de neurol. de France, Tunis, April 1912; Paludisme et, psychoses constitutionelles, Arch. de méd. et pharm., November 1922; cited by Anderson.[7]

5. Pasmanik, D.: Ueber Malariapsychosen, Wien. med. Wchnschr. **47**:518-519 (March 20) 1897.

6. Forrester, A. T. W.: Malaria and Insanity, Lancet **1**:16-17 (Jan. 3) 1920.

7. Anderson, W. K.: Malarial Psychoses and Neuroses: Their Medical, Sociological and Legal Aspects, London, Oxford University Press, 1927.

attention to the clinical and medicolegal aspects of the problem. In this country, clinical reports were made by Masson [8] and Turner.[9] Brill and Pellicano [10] described a reversible organic psychosis in a case of malignant malaria, in which the patient made a quick recovery with the early administration of quinacrine hydrochloride (atabrine).

Neuropathologic investigations of cerebral malaria have also been carried out in conspicuous numbers. Classic is the work of Cerletti,[11] who paid special attention to the vascular changes. Bignami and Nazari [12] studied the punctiform hemorrhages frequently found in cases of cerebral malaria and interpreted them as due to diapedesis from collateral vessels. Dürck [13] described nodules in the brain, which he called "malaria granulomata." Marchiafava [14] classified the alterations in the central nervous system as intravascular, vascular and extravascular. Rigdon and Fletcher [15] studied the lesions occurring in the brain of a child who died in the acute stage of infection with Plasmodium falciparum and in the brains of monkeys, chicks and ducks infected with malaria. They found the lesions to be similar in human and in experimental cases and interpreted them as due to anoxemia. Several other studies, dealing with special aspects of this neuropathologic problem, have been carried out.

The purpose of this investigation is to reexamine this timely subject with the assistance of more modern neurohistologic methods, not used in previous researches. Furthermore, an attempt will be made to interpret the relation of these pathologic changes to the psychotic manifestations which at times complicate this illness.

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8. Masson, C. B.: Effect of Malaria on the Nervous System with Special Reference to Malarial Psychoses, Am. J. M. Sc. **168**:334-371 (Sept.) 1924.

9. Turner, C. C.: The Neurologic and Psychiatric Manifestations of Malaria, South. M. J. **29**:578-586 (June) 1936.

10. Brill, N. Q., and Pellicano, V. L.: Estivoautumnal Malaria with Frontal Lobe Syndrome, J. A. M. A. **121**:1150-1152 (April 3) 1943.

11. Cerletti, U.: Die histopathologischen Veränderungen der Hirnrinde bei Malaria Perniciosa, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1910, vol. 4, pp. 169-266.

12. Bignami, A., and Nazari, A.: Sulle encefaliti emorragiche e sulla patogenesi delle emorragie miliariche del cervello, Riv. sper. di freniat. **42**:109-130, 1916.

13. Dürck, H.: Ueber die mit herdförmigen Gliaproduktionen einhergehenden Erkrankungen des Zentralnervensystems, Arch. f. Schiffs- u. Tropen-Hyg. (supp.) **29**:43-76, 1925.

14. Marchiafava, E.: Pernicious Malaria, Am. J. Hyg. **13**:1-56 (Jan.) 1931.

15. Rigdon, R. H., and Fletcher, D. E.: Lesions in the Brain Associated with Malaria: Pathologic Study on Man and on Experimental Animals, Arch. Neurol. & Psychiat. **53**:191-198 (March) 1945.

MATERIAL AND METHODS

Three cases of cerebral malaria due to P. falciparum were studied. One hemisphere of the brain in each of cases 1 and 3 was fixed in solution of formaldehyde U. S. P. (1:10) and the other hemisphere in 80 per cent alcohol. The brain in case 2 was entirely fixed in solution of formaldehyde U. S. P.

Microscopic investigations were carried out with the following histologic methods: hematoxylin and eosin, for general study; the technics of Nissl for nerve cells, of Giemsa for parasites, of Bodian for neurofibrils, of Ramón y Cajal (Globus-Penfield modification) for astrocytes, of del Río Hortega and Stern (Weil-Davenport modification) for microglia, of Weigert for elastic tissue and of Spielmeyer and Weil for myelin sheaths; sudan III, for fat; the Mallory and Van Gieson stain for connective tissue, and the Turnbull stain for iron. In addition, the following recently devised methods were used: the Eros stain for vascular pattern [16] and the Tomlinson and Grocott [17] stain for malarial parasites. Neumann's [18] modification of the Nissl method for material fixed in solution of formaldehyde U. S. P. was used in case 2.

Sections stained with the Eros method for the vascular pattern were particularly useful because they permitted the study of the punctiform hemorrhages in the three spatial dimensions and allowed a differentiation of the erythrocytes, which appeared red, and the malarial pigment, which appeared black. No such differentiation would have been possible with the Pickworth benzidine method. The Tomlinson and Grocott method was successful in only a few sections. Many sections were treated with ammonium sulfide for removal of the malarial pigment, as suggested by Tomlinson and Grocott, but were later stained with ordinary methods.

In preparation of the material in case 1, frozen sections, 120 to 200 microns thick, were cut, dehydrated and mounted in balsam without being stained. With these preparations it was possible to study the distribution of the malarial pigment, which was of natural color. Inasmuch as the pigment was almost completely contained within the vessels, the course of the latter was well outlined. Thus, the angioarchitecture in this case could be studied in these sections.

For sake of brevity, only cases 1 and 2 will be reported here in detail. Case 3 was essentially similar to case 2, except that the lesions were less pronounced.

REPORT OF CASES

CASE 1.—*Clinical Summary.*—The patient was found unconscious on a road which leads to the Ecuadorian region of the Amazon River, where malaria is endemic. He was a man apparently 20 to 22 years of age, of mixed white and Indian blood, but predominantly Indian. He was immediately taken to the hospital Eugenio Espejo, of Quito, Ecuador, where he arrived at 11 p. m. On admission, he was in a state of coma, from which he never aroused. The skin and the scleras were yellowish. The liver was enlarged, its lower border extending 4 cm. below

16. Eros, G.: Method for Fuchsin Staining of the Network of Cerebral Blood Vessels, Arch. Path. **31**:205-219 (March) 1941.

17. Tomlinson, W. J., and Grocott, R. G.: A Simple Method of Staining Malaria Protozoa and Other Parasites in Paraffin Sections, Am. J. Clin. Path. **14**:316-326 (June) 1944.

18. Neumann, M. A.: A Rapid Method for the Differentiation of Nerve Cells in Old Formalin Fixed Material, J. Neuropath. & Exper. Neurol. **1**:348-350 (July) 1942.

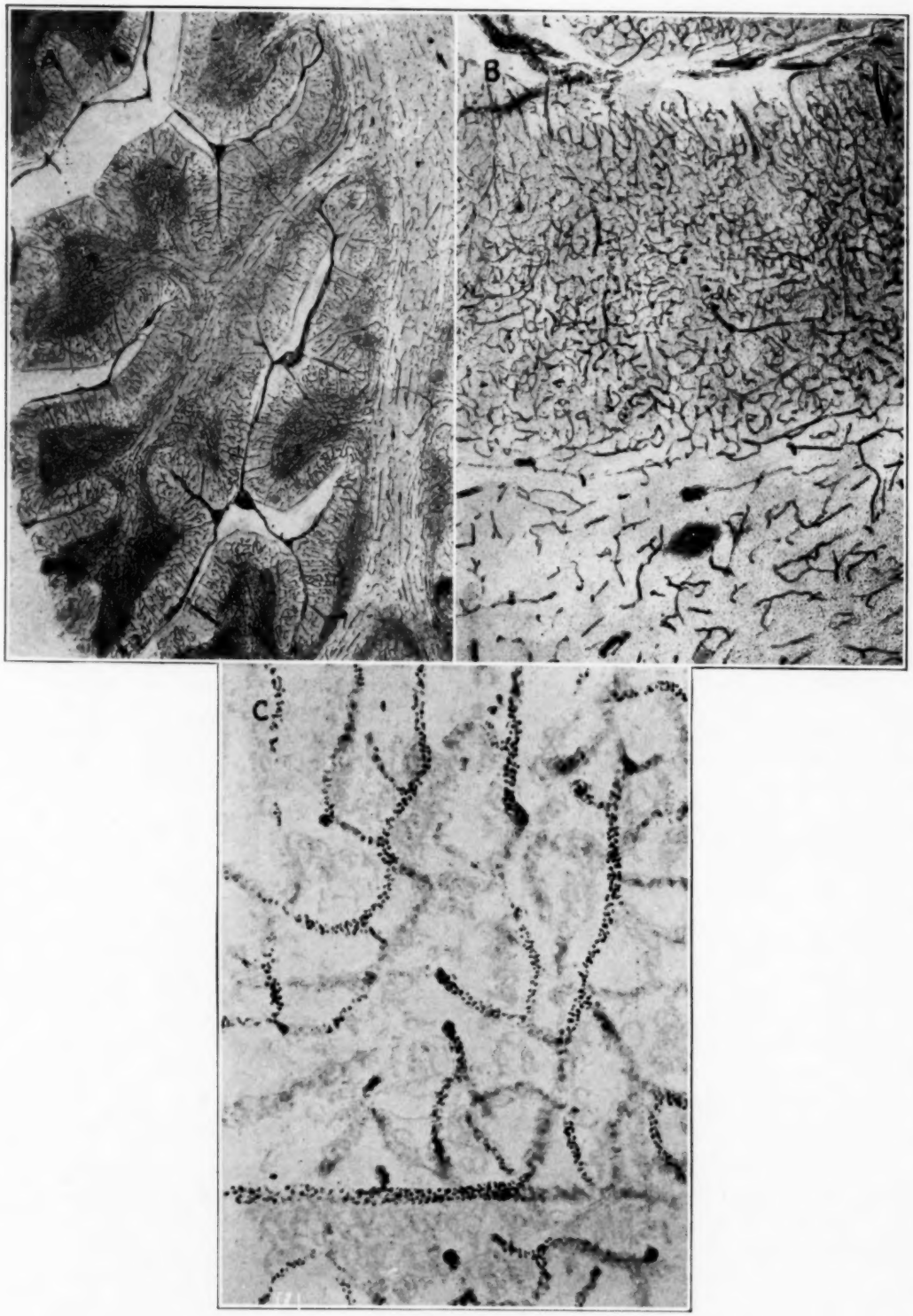

Figure 1

(See legend on opposite page)

the costal margin. The spleen could not be palpated. Smears of blood revealed trophozoites of the P. falciparum type. The patient died the following morning at 3 a. m. Unfortunately, no relative came to the hospital or could be reached by mail, so that no anamnestic data are available. However, on account of the condition in which the patient was found, it was felt that the illness had had an acute course.

Necropsy.—Autopsy was performed eleven hours after death. The bases of the lungs were congested and edematous. The liver was enlarged and friable. The cut surface appeared yellowish. The myocardium was flabby and yellow. The spleen was slightly enlarged. The kidneys were congested. The brain presented external hydrocephalus and diffuse edema. When the cerebral hemispheres were cut in transverse sections, numerous tiny hemorrhagic spots were noted.

Microscopic Examination of the Brain.—The histologic features presented by this case may be divided into four categories: changes involving (1) the blood vessels and their content and changes affecting (2) the nerve cells, (3) the glia and (4) the myelin sheaths.

The first category of changes was by far the most pronounced. Thick, unstained sections showed a tremendous amount of malarial pigment. Since this pigment was almost exclusively contained within the blood vessels, it beautifully outlined the whole cerebral and cerebellar angioarchitecture, which appeared in these unstained sections almost as distinctly as in sections prepared with stains specific for the vascular pattern or with injection methods (fig. 1). When the same sections were examined at higher magnification (fig. 1 *C*), it was noted that the dots of pigment were almost uniformly diffused in the capillaries. However, at certain points the black dots appeared particularly condensed as though they would form small plugs. This was observed especially where branches were given off or where the vessels made a sharp curvature. In some areas it was also possible to recognize the presence of small hemorrhages, which appeared as gray areas surrounding capillaries (fig. 1 *B*). These gray areas consisted of accumulated pigment, disclosing thus that even parasitized red cells could be extravasated into the nerve tissue.

In Eros sections it was possible to distinguish the two chief contents of the vessels, namely, the dots of pigment, which appeared black, and the erythrocytes, which stained red. Inasmuch as the malarial condition had caused an anemic state and the red cells were decreased in number and partially dehemoglobinized, the vessels did not appear as intensely red as in sections prepared from normal brains. The same sections disclosed the increased tortuosity of the vessels in the perivascular space and the presence of a large number of small hemorrhages. These

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EXPLANATION OF PLATE.

Fig. 1 (case 1).—Photomicrographs from unstained frozen sections, 120 to 200 microns thick. The malarial pigment, which is contained in the vessels, outlines the vascular pattern.

A (low magnification), cerebellar angioarchitecture. *B* (low magnification), section from a cerebral area, showing the difference in the vascular pattern in the cortex (upper part of the picture) and in the white matter (lower part). In the white matter it is possible to recognize a small hemorrhagic area, represented by a group of extravasated dots of pigment. *C*, section from a cortical area (medium magnification), revealing that the coloration is due to the granules of malarial pigment contained in the capillaries.

hemorrhages were particularly numerous in the subcortical white matter (fig. 2), but occasionally they were encountered in the cortex itself. In the cerebellum they were by far more frequent in the molecular layer of the cortex. The cortical hemorrhages were generally ill defined and consisted of red cells extravasated by diapedesis (fig. 3). In the white matter the hemorrhagic areas were generally

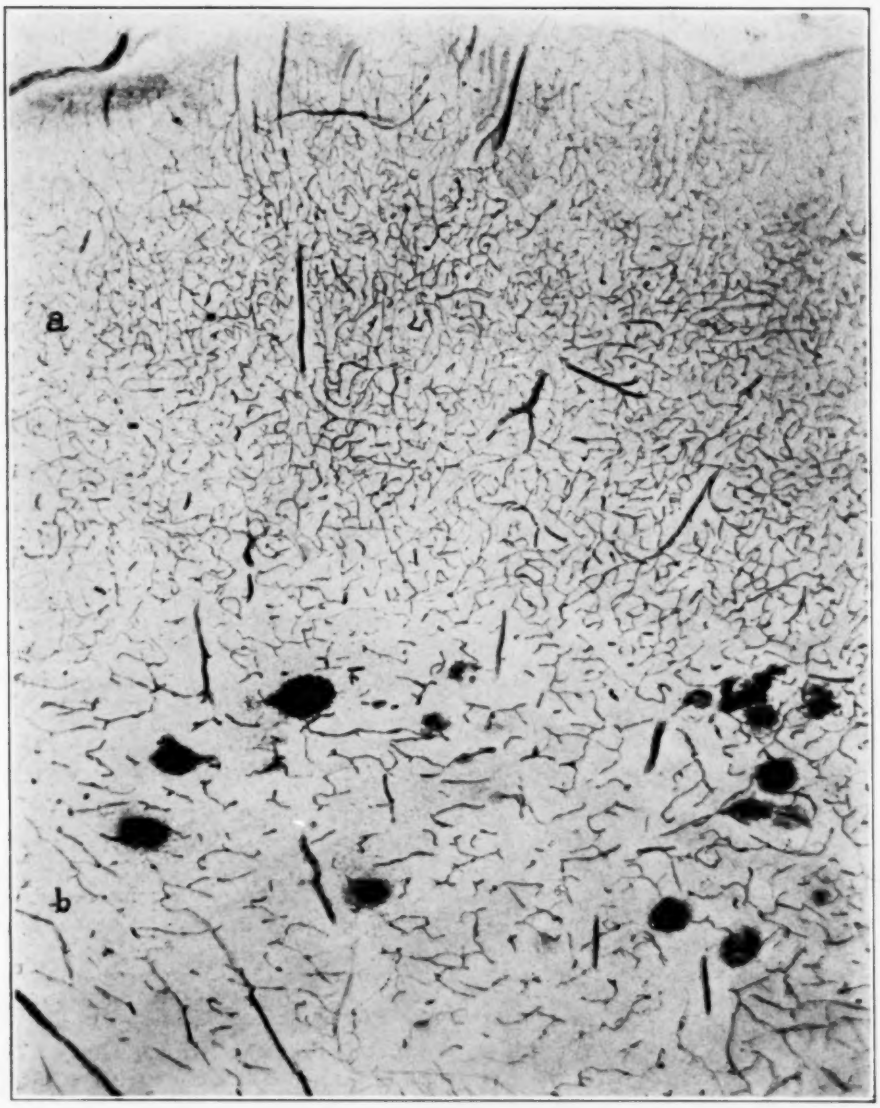

Fig. 2 (case 1).—Small hemorrhages in the subcortical white matter. The upper part of the picture (*a*) shows the vascularization of the cortex; the lower part (*b*) that of the white matter. Eros method; low magnification.

roundish. In the center of many of them one could observe a capillary plugged with dots of pigment (fig. 4 *A* and *B*). These dots obviously caused occlusion of many capillaries. In some instances the dots of pigment appeared so numerous

at the point of occlusion as to cause an enlargement and distention of the capillary (fig. 4 *A*). In several instances the extravasated red cells surrounded closely the occluded vessel and were in immediate contact with its wall (fig. 4 *A*). Oftener it was possible to distinguish around the capillaries a clearer central area, which contained fewer red cells, and a concentric peripheral area, where the red cells and the black dots were more numerous (fig. 4 *B*). In still other cases the clearer area was almost entirely deprived of blood cells, which were located in the peripheral area (fig. 4 *C* and fig. 8 *A*). Since Eros sections visualized the capillaries in the three spatial dimensions, it was possible to rule out the possibility that the extravasated cells were coming from collateral capillaries surrounding the hemorrhagic

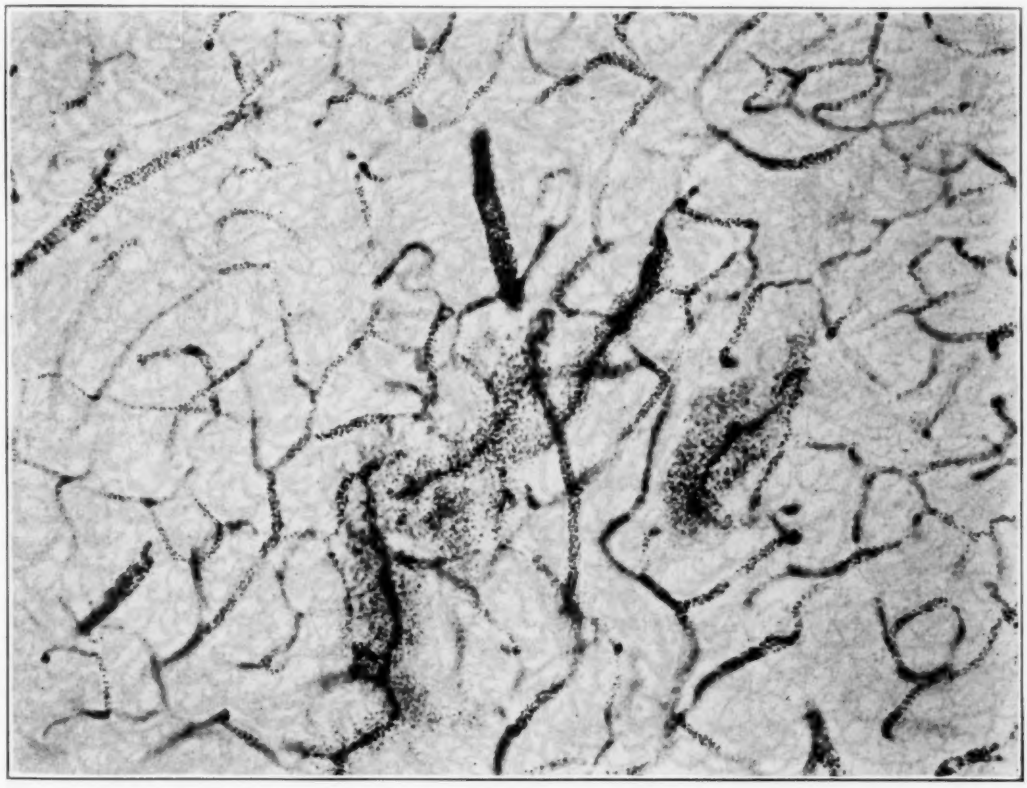

Fig. 3 (case 1).—Diapedesis from cortical capillaries. The dots of pigment may be distinguished from the red cells, which are less intensely and less distinctly stained. Eros method; low magnification.

area. I could convince myself that in almost all instances the red cells had extravasated from the occluded central capillary, either above or below the point of occlusion. No occlusion of medium or large vessels was seen in this case. The Eros stain revealed that in the larger vessels of the meninges and of the brain the dots of pigment (and therefore the parasites) were located only at the periphery of the lumen, close to the vascular wall.

Sections prepared with other methods confirmed the striking involvement of the vascular system observed in Eros preparations. Sections stained with hematoxylin and eosin and with the Nissl method and examined with low magnifi-

cation revealed a notable increase in blood vessels. Such an increase in blood vessels, however, might probably be more apparent than real, since the blood vessels were better evidenced on account of their engorgement and the productive changes in their walls. The increase in blood vessels was also noted in the white matter, in addition to the hemorrhages already described and to perivascular necrotic foci, to be described later. The medium-sized vessels appeared more tortuous than usual and occasionally rotated on their axis, so that the secondary branches were twisted. The new formation of pockets of vessels, as described by Cerletti, could easily be detected in sections stained with the Mallory aniline blue method. One could see bundles of newly formed capillaries within a single perivascular space (fig. 5 *B*). On examination with a high power lens the vessels showed interesting features both in their walls and in their lumen. The capillaries disclosed conspicuous proliferation of the endothelial cells. In the vessels in which the different coats were distinguishable both intimal and adventitial cells appeared stimulated to proliferation by the malarial infection. The new-formed endothelial cells of both meningeal and cerebral vessels were often seen projecting into the lumen. Often they were seen in the act of detaching or as already detached from the wall and entering the free circulation. Parasites were occasionally seen attached to the endothelial cells but never ingested by them. The adventitial cells presented changes involving the nucleus more than the cytoplasm. The nuclei were enlarged and rich in chromatin; often they were elongated or oval. At times the chromatin was gathered at the periphery of the nucleus in a ringlike distribution.

The majority of the red cells of the cerebral vessels appeared to be parasitized (fig. 5 *A*), as revealed by the fact that they contained a dot of pigment at one extremity of the cytoplasm. Parasites were generally obscured by the pigment and could not be seen. However, a few sections, prepared with the Tomlinson-Grocott method, showed a few clear trophozoites. Other sections, stained with hematoxylin and eosin, after the pigment had been dissolved with ammonium sulfide, also showed some clear trophozoites. However, since each mass of pigment stands for a parasite, the gravity of the infection could be easily evaluated in this case. A few schizonts and crescents were also seen. Monocytes were likewise numerous in all sections examined and showed a great affinity for basic stains, no matter what method was used. The large meningeal vessels contained a larger number of parasitized monocytes but by far a smaller number of infected erythrocytes.

The cortical architecture was as a rule well preserved. The nerve cells presented diffuse changes. Many of them presented unduly well visualized processes. The most frequently encountered alterations consisted of transitional stages in the direction of the ischemic type of degeneration or of clearcut ischemic changes (fig. 6). The acute swelling of Nissl could be studied well in the motor area, especially in Betz cells located near capillaries full of parasites (fig. 7 *A* and *C*). These cells presented swelling of the cytoplasm and dissolution of Nissl bodies. Some cells exhibited swelling, central chromatolysis and dislocation of the nucleus, indicating a process of retrograde degeneration (fig. 7 *B*). Severe types of degeneration and pyknotic changes were not encountered. The cellular alterations described were accompanied with a mild increase in satellitosis.

Changes in the glia and the myelin sheaths were noted in connection with small necrotizing foci, especially in the subcortical white matter. These foci surrounded capillaries and appeared to coincide in their distribution, extension and architecture with areas in which small hemorrhages had presumably taken place.

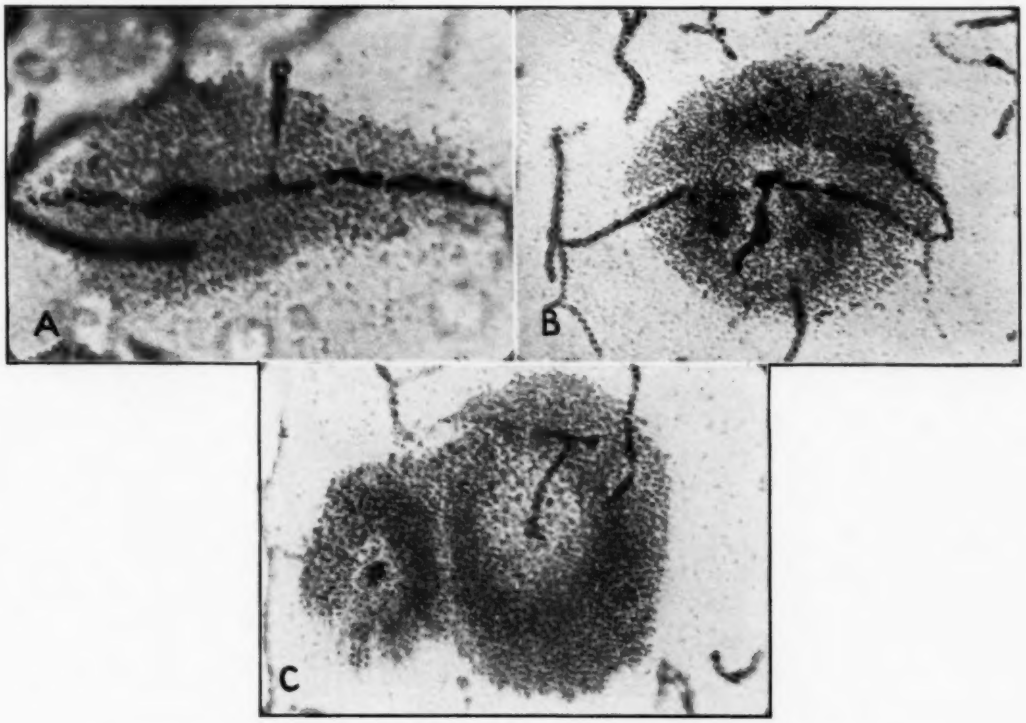

Fig. 4 (case 1.)—Color photomicrographs (Eros method; high magnification). *A*, small hemorrhage, in the center of which is a capillary, loaded with parasites. At the point of occlusion the large amount of pigment distends the capillary. *B*, small hemorrhage crossed by a capillary occluded with a plug of malarial pigment. The point of occlusion is centrally located and is clearly visible. In the central area rarefaction of the red cells has begun. *C*, two small hemorrhages, in the central area of which the red cells have almost entirely disappeared.

In the center of them it was generally possible to recognize a capillary loaded with parasites (fig. 8 *B*). The capillary was surrounded by an area of demyelination, as revealed by the Spielmeyer and Weil stain. A concentric peripheral area was also observed, in which at times red cells, but more often glia nuclei, were gathered. When these glia nuclei were present, formations similar to granu-

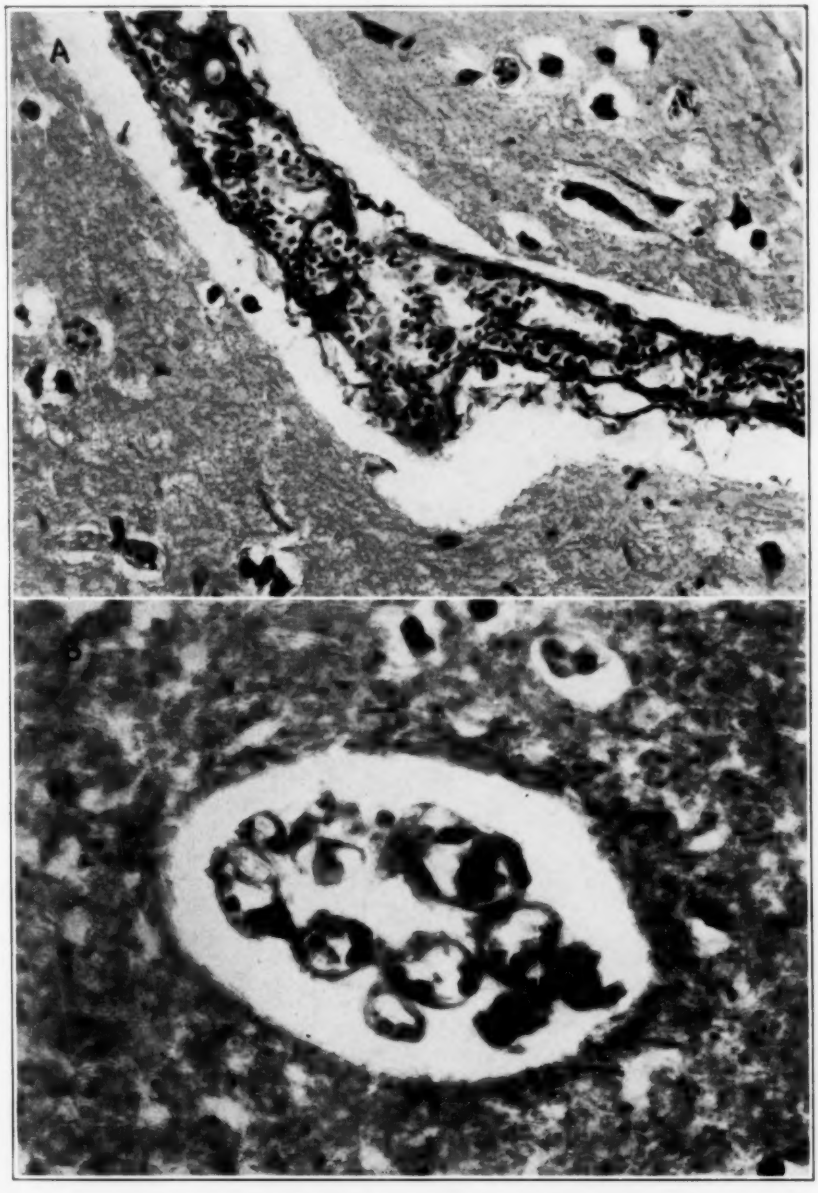

Fig. 5 (case 1).—*A*, cerebral vessel loaded with malarial parasites and pigment. Notice also the enlarged perivascular space. Giemsa stain; medium magnification. *B*, pocket of newly formed capillaries within a single perivascular space. Mallory stain; high magnification.

lomas were observed (fig. 8 *C*). The white matter appeared altered, not only on account of the presence of these pseudogranulomas, in varying stages of formation, but also because the tissue was extremely edematous and loose.

Stains specific for glia did not reveal changes in addition to those described in relation to the pseudogranulomas. Sections stained with prussian blue did not disclose an abnormal amount of iron.

No hemorrhages, demyelinating areas or pseudogranulomas were noted in the brain stem or in the three upper cervical segments, which were the only part of the spinal cord available for study.

Case 2.—*Clinical Summary.*—G. M., a 6 year old orphan child, of mixed white and Indian blood, was taken to the Milagro Hospital by his neighbors. They had

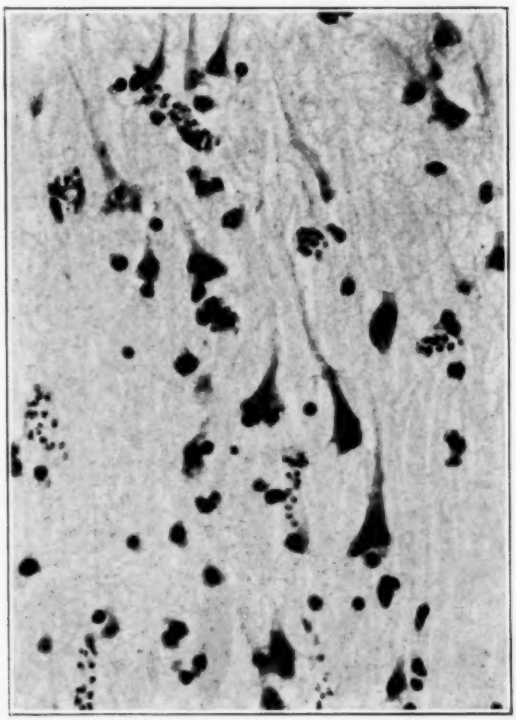

Fig. 6 (case 1).—Ischemic changes in nerve cells. Nissl stain; medium magnification.

found him in convulsions and lying on the ground in a street of the town. They stated that for several days prior to his admission the child had had fever and had undergone convulsive seizures.

The patient entered the hospital on May 2, 1942 at 2:30 p. m. On admission he was noted to be in a state of malnutrition and presented a rachitic rosary. He was unconscious. His temperature was 40.6 C. (105.1 F.). Examination of the lungs revealed rales in the upper and middle portion. The abdomen was tympanitic. The spleen could be palpated 5 cm. below the costal margin and was hard in consistency. The liver also could be palpated 2.5 cm. below the costal margin. The tendon reflexes were increased. The Babinski sign was elicited on both sides but not

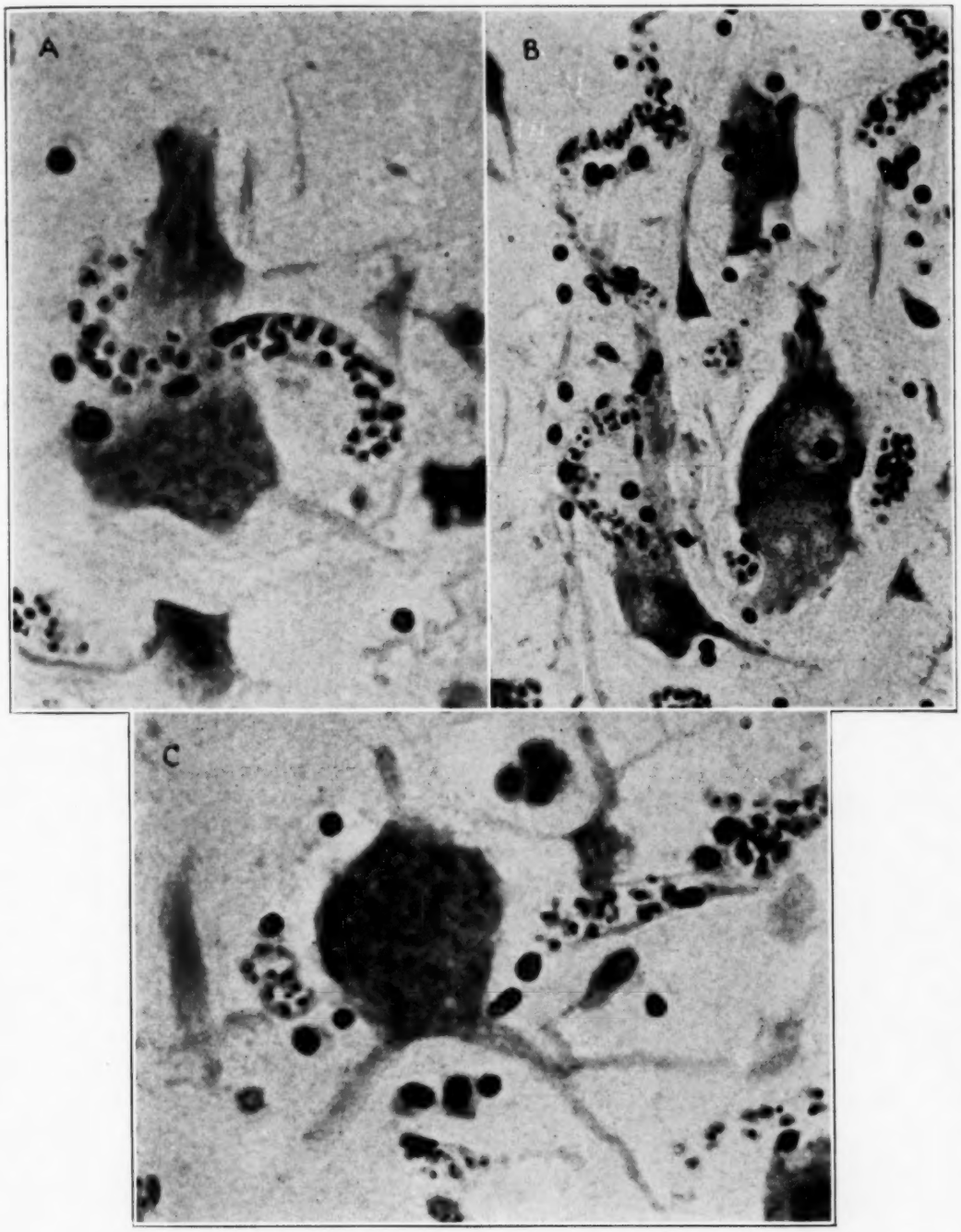

Fig. 7 (case 1).—*A*, Betz cell, surrounded by a capillary loaded with parasites. Notice the dissolution of tigroid substance in the cytoplasm of the nerve cell. *B*, Betz cells, showing retrograde (axonal) degeneration. The nucleus is displaced, and the tigroid substance is dissolved in the center of the cell but preserved at the periphery. Notice also the large number of parasites in the neighboring capillaries. *C*, ganglion cell of the motor area, showing acute swelling. Nissl stain; high magnification.

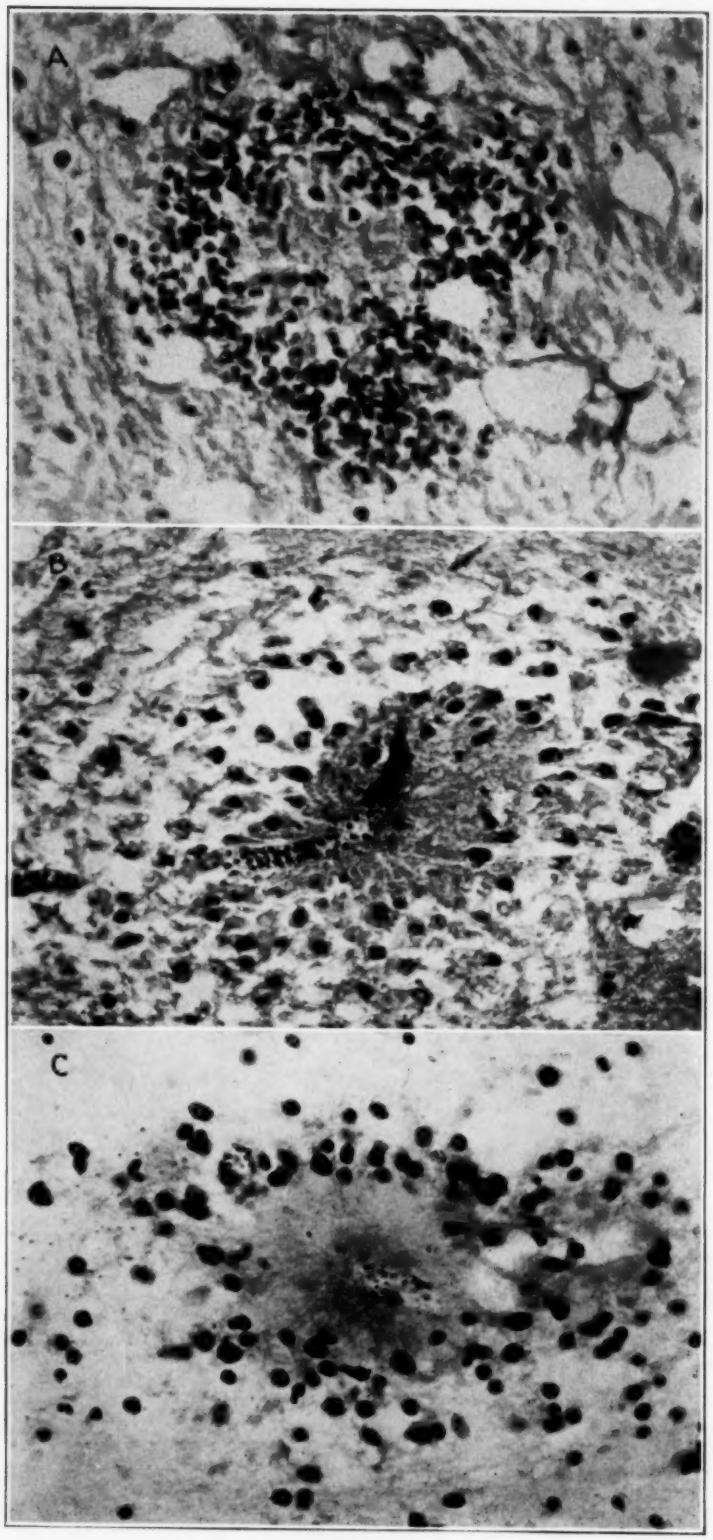

Figure 8

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consistently. The patient underwent convulsive seizures approximately every thirty minutes, without acquiring consciousness in the intervals. Examination of the blood could not be made. The child died at 4:30 p. m. on the day of admission.

Necropsy.—Autopsy was performed one and a half hours after death. The bases of the lungs and the abdominal organs were congested. The liver and the spleen were considerably enlarged. The spleen was dark and of hard consistency, and its capsule was distended. When the skull was opened external hydrocephalus was noted. The leptomeninges were slightly clouded. The meningeal and the cerebral blood vessels were dilated and congested.

Microscopic Examination of the Brain.—The histologic alterations in this case were by far less pronounced than in the previous one. Nevertheless, it was possible to recognize in every section studied diffuse and conspicuous involvement of the blood vessels. The capillaries were increased in number, both in the white and in the gray matter. Pockets of new-formed capillaries were often observed, especially in sections prepared with the Mallory aniline blue method. All the vessels appeared dilated and congested. Many of them were tortuous and were surrounded by an enlarged perivascular space. In almost all capillaries the presence of parasites, with their granules of pigment, was noted. However, the parasites were by far less numerous than in the previous case, so that in thick, unstained sections, prepared as previously described, the vascularization could not be visualized. The endothelial changes were similar to those in the previous case and in many regions were even more pronounced. Both meningeal and cerebral vessels exhibited conspicuous proliferation of endothelial cells, which became detached from the intima and entered the free circulation (fig. 9 *A* and *B*). The adventitial cells also showed conspicuous stimulation. They were increased in size and presented a large and hyperchromatic nucleus. No hemorrhages were noted in this case. Sections stained with the Eros method disclosed clots of nonparasitized red cells within the capillaries (fig. 10). It seemed as though the erythrocytes would easily agglutinate within the vessels. There was no extravasation of cells, however, around these clots or damage of the myelin sheaths, though the blood supply was diminished, as revealed by the fact that the surrounding vessels appeared slightly less impregnated with the Eros stain.

The cortical architecture was well preserved throughout. The nerve cells exhibited diffuse changes. Many of them presented disintegration of Nissl bodies and unduly well visualized and tortuous processes. In many instances typical ischemic changes were observed.

Glial reaction was evident throughout. Both the gray and the white matter exhibited an increase in glia nuclei. Such increase, however, was particularly evident around the capillaries of the white matter (fig. 11 *A*). Enlarged nuclei

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EXPLANATION OF PLATE.

Fig. 8 (case 1).—Formation of a pseudogranuloma. (*A*) In a small subcortical hemorrhage, the red cells have almost completely disappeared from the center of the area (only a few are left in radial positions) but are still numerous at the periphery. Mallory stain; medium magnification. (*B*) The red cells have disappeared from the peripheral area also. This area appears edematous and of loose consistency and shows proliferation of glia cells. Note also a central capillary loaded with parasites. Giemsa stain; medium magnification. (*C*) The pseudogranuloma is now almost formed. At the center one sees in cross section a capillary loaded with parasites. A necrotic central area is surrounded by a peripheral cuffing consisting predominantly of glia cells. Nissl stain; medium magnification.

and ameboid elements were frequently encountered, especially in the sixth layer of the cortex and in the subcortical white matter. Cajal sections showed hyperplasia and hypertrophy of the astrocytes. A single astrocyte exhibited at times

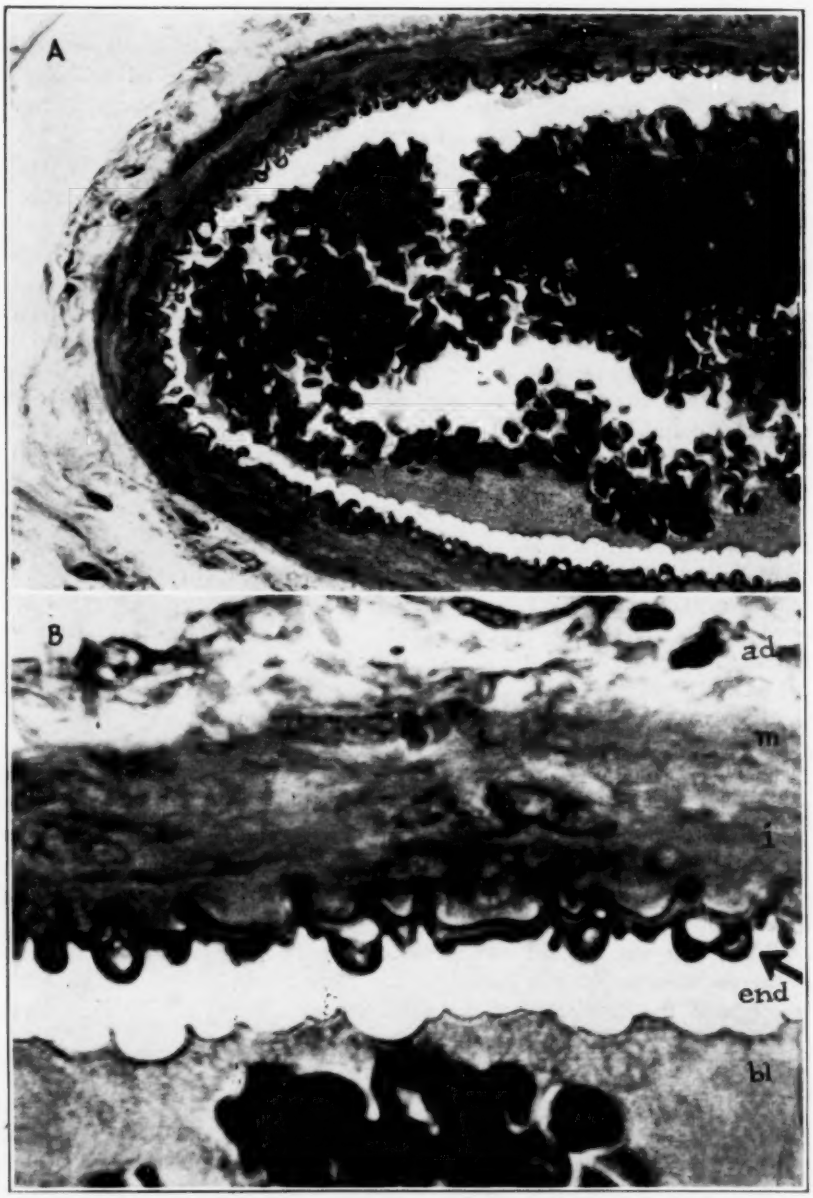

Fig. 9 (case 2).—Sections stained with hematoxylin and eosin.

A, (low magnification), meningeal artery, showing pronounced desquamation of endothelial cells from the intima.

B, (high magnification), detail from *A*. Here, *ad* indicates adventitia; *m*, media; *i*, intima, with well defferentiated elastica; *end*, endothelial cells becoming detached from the intima and entering the free circulation, and *bl*, clotted blood.

several vascular feet, which reached various capillaries (fig. 11 *B*). No pseudogranulomas or areas of demyelination were noted in the white matter.

COMMENT

The punctiform hemorrhages, as described in case 1, and the histologic processes which they subsequently undergo are perhaps the outstanding features of cerebral malaria. The dependence of these hemorrhagic areas on the vascular pattern could be easily established in case 1. In fact, they were found almost exclusively in the molecular layer of the cerebellum and in the white matter of the brain, especially in the subcortical areas. Pfeifer,[19] Cobb [20] and others, who have studied

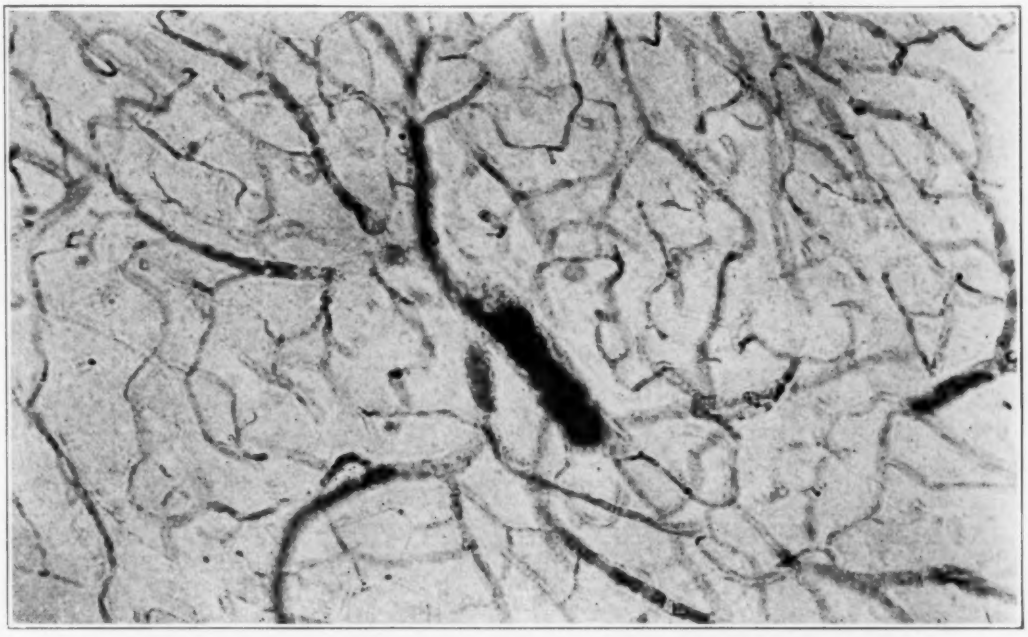

Fig. 10 (case 2).—Clumping of red cells in cortical capillaries. Note a few granules of malarial pigment in several vessels.

the angioarchitecture of the nervous system with injection methods, have reported that the vascularization of the molecular layer of the cerebellum is much poorer than that of the granular layer and that the same is true of the vascularization of the cerebral white matter as compared with that of the gray matter. When a blood vessel of a

19. Pfeifer, R. A.: Die Angioarchitektonic der Grosshirninde, Berlin, Julius Springer, 1928.

20. Cobb, S.: The Cerebrospinal Blood Vessels, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2.

poorly supplied area is occluded, collateral circulation cannot always be established. Therefore, the vascular walls near the point of occlusion may undergo changes which will permit diapedesis, and the tissue supplied by the occluded vessel may undergo degenerative changes.

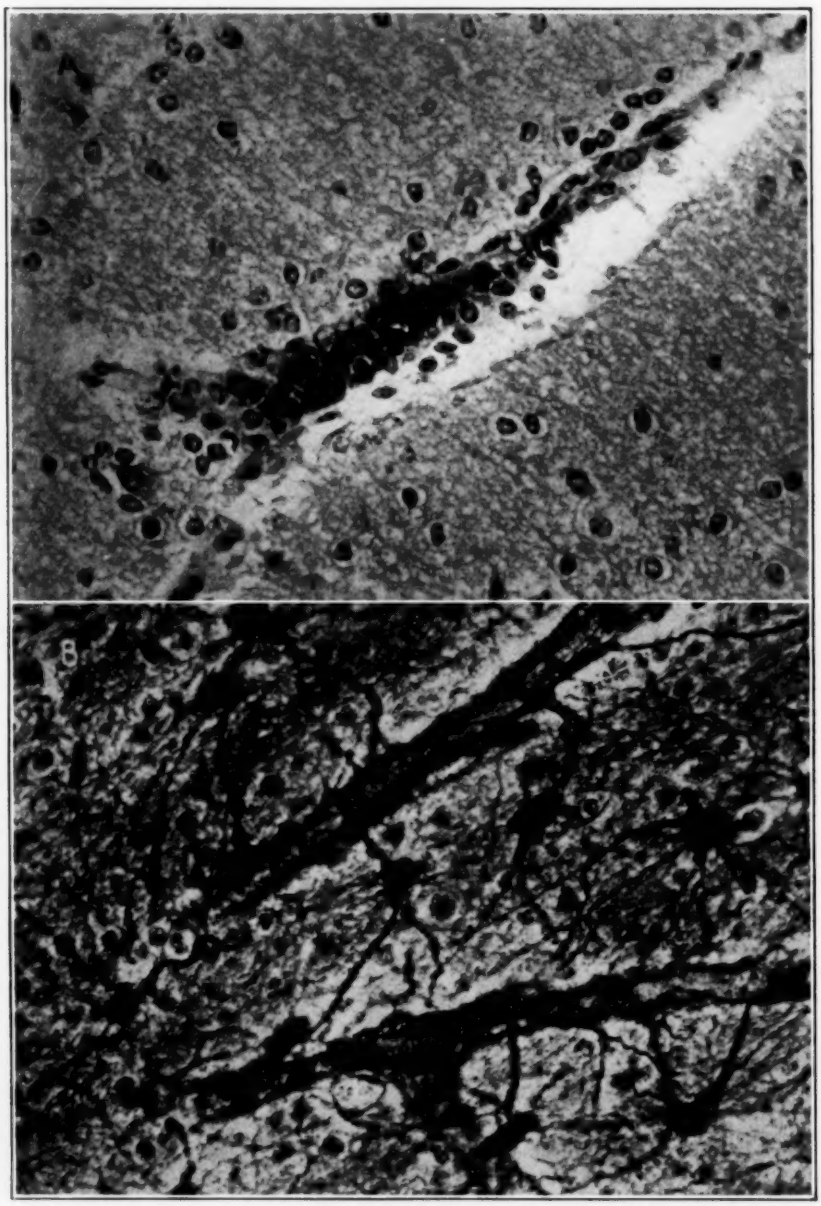

Fig. 11 (case 2).—*A*, increased number of glia nuclei around a blood vessel. Hematoxylin and eosin; medium magnification. *B*, hypertrophy and hyperplasia of macroglia cells. Astrocytes send expansions to more than one vessel. Cajal stain (Globus modification); medium magnification.

In case 1, as well as in others reported in the literature, the hemorrhagic lesions were predominantly observed in poorly supplied regions, which were near the point of transition into richly supplied areas. The occlusions mentioned were due to plugs of granules of pigment, parasitized erythrocytes and newly formed endothelial cells. These plugs acted as real emboli and determined embolic lesions. The punctiform hemorrhages were generally seen around occluded capillaries. In a few instances complete occlusion could not be found, but the quantity of pigment was probably sufficient to slow the circulation and to produce alterations of the vascular walls to such a degree as to permit diapedesis. The hemorrhages consisted of a roundish cuffing of extravasated red cells. In sections stained with the Eros method and in thick, unstained sections it was possible to recognize that several of the extravasated red cells contained granules of pigment and were therefore parasitized. This is important because Bignami and Nazari [12] claimed that parasitized red cells never extravasate, presumably because their motility is impaired.

The hemorrhages were of two types. The first type consisted of red cells, which surrounded closely the capillary. In the second type the capillary was surrounded by a pale area in which no, or very few, red cells were present. Sections stained with the Spielmeyer and Weil method disclosed that the pale area was undergoing demyelination. I have observed all gradations between the first and the second type of hemorrhages, and I am under the impression that the second type represents a more advanced stage. The red cells start to undergo rarefaction in the demyelinating area, from which they finally disappear, and are left only in the peripheral area. I feel that the red cells in the central area disintegrate gradually because in a subsequent stage they disappear also from the peripheral area and are replaced with glia cells. When these glia cells gather in the peripheral area, one sees those features which Dürck [13] called malarial granulomas. These foci consist of a central blood vessel surrounded by a demyelinating area, which is, in turn, surrounded by an area of gliosis. From the foregoing description it is obvious that these lesions are the result of the hemorrhages and that the glial proliferation is a reparative reaction to the local damage. No inflammatory changes are noted. It seems incorrect, therefore, to call these nodules granulomas, as it would be to designate the so-called Lichtheim plaque of pernicious anemia as a granuloma. However, if one wishes to emphasize the apparent similarity of these nodules to granulomas, one might call them "malarial pseudogranulomas."

Bignami and Nazari and others maintained that the hemorrhagic lesions are small infarcts and that the hemorrhagic red cells have

extravasated from collateral capillaries, located in the vicinity of the occluded vessel. Such is, in reality, the impression which one gets in studying sections prepared with the usual methods. However, if one uses thick sections, which permit visualization of the capillaries in the three spatial dimensions, one easily recognizes that the extravasated red cells do not come from neighboring capillaries but come only from the central vessel. A process of diapedesis occurs above and below the point of occlusion or partial occlusion. The absence of red cells in the pale area surrounding the capillary is explained by the fact that the erythrocytes have disappeared in this area, which is undergoing demyelination and at times necrosis. Often the occluded vessel has a tortuous course within the necrotic focus, so that one may receive the impression that another capillary is undergoing a process of diapedesis. In a few instances several neighboring capillaries presented diapedesis because they were all occluded. No occlusion of precapillaries or of medium or large vessels was observed.

These perivascular lesions caused by embolic plugs remind one of the experimental and other pathologic studies carried out by Putnam and his school [21] in an attempt to explain the pathogenic mechanism of multiple sclerosis. The lesions described in the present report undoubtedly demonstrate that plugs occluding capillaries may cause demyelinating areas and to a certain extent corroborate Putnam's theory. The fact that the lesions occur predominantly in the subcortical white matter is also a characteristic common to many cases of multiple sclerosis and may indicate that in the latter disease also the location of the lesions is determined by the vascular pattern. These demyelinating areas, however, differ in the two conditions, inasmuch as perivascular infiltrations of lymphocytes, which are often found in cases of multiple sclerosis and which may be considered as the expression of an allergic (Ferraro [22]) or an inflammatory reaction, are absent in cerebral malaria. In addition, the perivascular pathologic process in malaria more often than in multiple sclerosis goes beyond a state of demyelination to complete focal necrosis with little glial reparative reaction. Further-

21. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591-1596 (Nov. 28) 1931. Putnam, T. J.: The Pathogenesis of Multiple Sclerosis: A Possible Vascular Factor, New England J. Med. **209**:786-790 (Oct. 19) 1933; Lesions of "Encephalomyelitis" and Multiple Sclerosis: Venous Thrombosis as the Primary Alteration, J. A. M. A. **108**:1477-1480 (May 1) 1937. Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:799-812 (April) 1938.

22. Ferraro, A.: Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain, Arch. Neurol. & Psychiat. **52**:443-483 (Dec.) 1944.

more, in reviewing the literature on malaria, one is struck with the relative scarcity of pathologic reports on the spinal cord. This may be due, however, to the fact that serial studies of the spinal cord have never, to my knowledge, been carried out in cases of malaria. Small foci along the long tracts of the spinal cord may give rise to obvious clinical symptoms and yet may remain unnoticed if serial sections are not made. As a matter of fact, many authors have reported clinically the occurrence in the course of malaria of syndromes resembling multiple sclerosis (Torti and Angelini,[23] Canellis,[24] Triantaphyllidès,[25] Papastrategakis,[26] and Parrot [27]). In the American literature, Spiller [28] reported 1 such case, both from a clinical and a pathologic point of view. All the foregoing observations seem to indicate that embolic plugs, similar to those encountered in cerebral malaria, may constitute a factor in the mechanism of multiple sclerosis.[29]

In case 2 no actual thrombi or emboli were observed. However, Eros sections revealed many intravascular clumpings of nonparasitized red cells (fig. 10). Some capillaries were filled with cylinders of tightly packed cells. Knisely and associates [30] observed the same phenomenon in cinematographic studies on monkeys infected with Plasmodium knowlesi. These plugs, or clumpings, were probably caused by the increased viscosity of the red cells, reported to occur in the course of malaria by numerous authors, and presumably did not arrest the circulation. In fact, no hemorrhages, necrotic foci or pseudogranulomas were noticed in this case. These clumpings of red cells, however, may cause a transitory state of ischemia, which, in turn, may

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23. Torti, A., and Angelini, A.: Infezione malarica cronica coi sintomi della sclerosi a placche, Riforma med. **12**:817-825 (June) 1891.

24. Canellis, S.: Étude sur un cas de sclérose en plaques disséminées à la suite d'une intoxication par le miasme paludéen, Gaz. hebd. de méd. **24**:554-555 (Aug. 26) 1887.

25. Triantaphyllidès: Pseudo-sclérose en plaques d'origine palustre, Arch. de neurol. **26**:232-234 (Sept.) 1893.

26. Papastrategakis, C., cited by Anderson.[7]

27. Parrot, L. M.: Note sur un cas de sclérose en plaques d'origine paludéenne, Rev. de med. et d'hyg. trop. **6**:98-101, 1909.

28. Spiller, W. G.: A Case of Malaria Presenting the Symptoms of Disseminated Sclerosis, with Necropsy, Am. J. M. Sc. **120**:629-647 (Dec.) 1900.

29. This problem will be discussed more thoroughly in further contributions, in which the neuropathology of malignant malaria will be studied as an aid to explain the pathogenic mechanisms of other neurologic conditions of possible vascular origin.

30. Knisely, M. H.; Stratman-Thomas, W. K., and Eliot, T. S.: Observations on Circulating Blood in the Small Vessels of Internal Organs in Living Macacus Rhesus Infected with Malarial Parasites, abstracted, Anat. Rec. (supp.) **79**:90 (March) 1941.

be one of the factors responsible for the ischemic changes in the nerve cells.

No special consideration will be given in this investigation to the nature of the malarial pigment. The reader is referred to the studies of Morrison and Anderson.[31] It will be mentioned only that, in agreement with the observations of these authors, it seems from the present investigation that in the nervous system, too, the pigment is a morbid agent not because of its chemical qualities but because of its mechanical effect, inasmuch as it causes vascular occlusions or slowing of the circulation.

Mesodermal changes were present in marked degree in all cases, thus disclosing that they are an important feature of cerebral malaria, irrespective of the intensity of the illness. The adventitial cells of the meningeal and cerebral vessels were enlarged; the nuclei were rich in chromatin and had an increased affinity for basic stains. The endothelium lining the lumen of the vessels was also conspicuously stimulated. The endothelial cells were seen to be desquamating in large quantity and entering the free circulation. This phenomenon was observed not exclusively in capillaries, as reported by Bruetsch,[32] but also in large vessels. Many authors have attributed phagocytic activities to these endothelial cells (Barker,[33] Gaskell and Millar,[34] Seyfarth,[35] Thomson and Annecke,[36] Torrioli,[37]). On the other hand, Jaffé [38] reported that

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31. Morrison, D. B., and Anderson, W. A. D.: The Pigment of the Malaria Parasite, Pub. Health Rep. **57**:90-94 (Jan. 16) 1942; On the Role of Parasite Pigment in the Malaria Paroxysm, ibid. **57**:161-174 (Jan. 30) 1942. Anderson, W. A. D.; Morrison, D. B., and Williams, E. F., Jr.: Pathologic Changes Following Injections of Ferrihemate (Hematin) in Dogs, Arch. Path. **33**:589-602 (May) 1942. Anderson, W. A. D., and Morrison, D. B.: Role of Parasite Pigment (Ferrihemic Acid) in the Production of Lesions in Malaria, ibid. **33**:677-686 (May) 1942.

32. Bruetsch, W. L.: The Histopathology of Therapeutic (Tertian) Malaria, Am. J. Psychiat. **12**:19-65 (July) 1932; Activation of the Mesenchyme with Therapeutic Malaria, J. Nerv. & Ment. Dis. **76**:209-219 (Sept.) 1932.

33. Barker, L. F.: A Study of Some Fatal Cases of Malaria, Johns Hopkins Hosp. Rep. **5**:219-277, 1895.

34. Gaskell, J. F., and Millar, W. L.: Malignant Malaria in Macedonia, Quart. J. Med. **13**:387-426 (July) 1920.

35. Seyfarth, C.: Die Malaria, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 1, pp. 178-248.

36. Thomson, J. G., and Annecke, S.: Observations on the Pathology of the Central Nervous System in Malignant Tertian Malaria, with Remarks on Certain Clinical Phenomena, J. Trop. Med. **29**:343-346 (Oct. 15) 1926.

37. Torrioli, M.: La fagocitosi nella malaria, Riv. di malariol. **10**:321-347 (May-June) 1931.

granules of pigment are attached to, but not incorporated by, endothelial cells. Taliaferro and Mulligan,[39] in a particularly thorough study of the brains of rhesus monkeys during the terminal stage of infection with P. knowlesi, observed that phagocytosis by vascular endothelial cells was negligible as compared with that occurring in the spleen, liver and bone marrow. In this study, which was limited to the brain, I also observed that phagocytosis by endothelial cells was practically absent. The few instances in which it seemed to have occurred were equivocal. These observations, though not establishing a phagocytic action, do not disprove that these desquamated cells have a defensive action. It will be recalled here that Bruetsch [32] attributed to this endothelial desquamation the therapeutic action of malaria in dementia paralytica. He expressed the belief that the tremendous stimulation of endothelial cells first increases and subsequently decreases the permeability of the cerebral capillaries.

The nerve cells presented with special frequency three types of changes: The most common consisted of gradual alterations in the direction of the ischemic type of change. They were obviously due to the ischemia produced by the vascular occlusions and to the secondary anemia. Second in frequency was the acute swelling of Nissl. Third was the retrograde cell change, possibly due to interruption of the axons in the white matter. This last change was observed only in case 1, which was the only one in my series to present necrotic foci.

In case 2, glial hypertrophy and hyperplasia were conspicuous and widespread. Ameboid elements were frequently observed in the sixth layer of the cortex and in the subcortical white matter. As already described by Dürck,[13] conspicuous gathering of glia with nuclei was observed along the course of capilaries. These glial nuclei often formed a cuffing in a one cell layer for a long tract of the vessel. The changes of the glia described were by no means specific but might be interpreted in this case as a reaction to a deficient blood supply. The edema observed to a striking degree in all 3 brains must also receive particular attention.

If now one reconsiders the changes already described, it is possible to draw some general conclusions. First, however, it must be recalled that the 3 cases studied in this investigation presumably represented an acute type of malaria. If the course in these cases had been longer,

38. Jaffé, R. H.: The Reticulo-Endothelial System: Its Role in Pathologic Conditions in Man, Arch. Path. **4**:45-91 (July) 1927; cited by Taliaferro and Mulligan.[39]

39. Taliaferro, W. H., and Mulligan, H. W.: The Histopathology of Malaria with Special Reference to the Function and Origin of the Macrophages in Defence, Indian Medical Research Memoirs, no. 29, Calcutta, Thacker, Spink & Co., 1937, pp. 1-138.

additional alterations would undoubtedly have been observed. Some of the alterations here described seem to be reversible and compatible with clinical recovery following disappearance of the parasites and of the vascular blockages. Other alterations, on the contrary, especially some of those described in case 1, appear irreversible and may explain why, even after a clinical recovery, the patient may remain "a changed man" (Wilson [40]). One may also state that though malaria is due to a minor parasitic infection the histologic reaction in the brain is not inflammatory. The infection does respect as a rule the hematoencephalic barrier. The comparatively few parasites which are extravasated into the nerve tissue promptly perish. The majority of the extravascular lesions are caused by physical mechanisms (vascular occlusion and slowing down of the circulation).

Of course, not all the lesions have to be attributed to these mechanisms. Two other important factors play roles which cannot be overlooked: first, the intermittent hyperthermic state, and, second, the catabolic substances produced in the course of the illness. In experimental hyperthermia, in fact, both parenchymatous and interstitial changes have been found (Hassin [41]). Acute cell disease of Nissl has been described in rabbits in which the temperature was raised to 44 C. (111.2 F.). In cases of hyperthermia of longer duration hyperemia of blood vessels, swelling of endothelial cells and hemorrhages were also observed by Omorokow.[42] Though in malaria the temperature does not rise over 107 F., the hyperthermic state may have played a secondary role in the pathologic process in my cases. More difficult is it to determine the role played by the catabolic substances. Omorokow said it was possible that the lesions observed in his experimental cases might have been produced by the catabolic changes resulting from the hyperthermia.

What is the correlation between the cerebral changes described and the psychotic syndromes which sometimes complicate malaria or follow this illness even after apparent recovery? The literature on the psychotic complications of malaria is difficult to review on account of the different terminologies used in the various countries where the investigations were made. However, it seems to me that the most common psychotic conditions which have been described may be classified under four heads: (1) acute deliriums; (2) paranoid syn-

40. Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940, vol. 1.

41. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous Systems, Baltimore, William Wood & Company, 1933.

42. Omorokow, L.: Ueber den Einfluss hoher Temperaturen auf das Zentralnervensystem das Kaninchens, in Nissl, F., and Alzheimer, A.: Histologische und histopathologischen Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1913-1914, vol. 6, pp. 1-32; cited by Hassin.[41]

dromes; (3) typical psychoses, such as schizophrenia and manic-depressive psychoses, and (4) organic conditions.

The acute deliriums include conditions which have been designated by Anderson as "confusional psychoses" and which may terminate in "malarial coma." These deliriums are fundamentally similar to all the toxic-infective deliriums. They are distinguished, however, by their greater severity, by the more marked state of amnesia which they cause and by their frequent termination in a state of coma. Other differential characteristics are (1) periodicity of the symptoms in accordance with the febrile cycles and the sporulation of parasites; (2) possible epileptiform convulsions and other neurologic symptoms, and, finally, (3) a tendency to fall into a state of agitated melancholia.

The cases reported in this article do not offer many clinical details for study, but their histologic alterations may help to explain the symptoms in other cases. These cases, especially case 1, reveal that the malarial delirium should not be interpreted merely as a complication of a general illness, similar to the other organic-infective deliriums. Its severity may be attributed directly to the pathologic process in the brain, even if it is not as marked or as acute as that in case 1 (edema of the brain tissue, diminished blood supply, complete anemia of certain areas). The irritation of the nerve cells caused by neighboring plugs of pigment or by the parasites may explain the spasms, the convulsions and other neurologic symptoms. In this connection, it is worth while to mention that Meth [43] observed a tremendous number of epileptic patients in the malarial districts of Ecuador. Though he could not confirm his impression by a large number of examinations of the blood, he is inclined to believe that the epilepsy in these cases is due to chronic or to subacute malarial infections.

The second type of malarial psychoses consists of paranoid states, or what Anderson [7] called "delusional psychoses." They include conditions which in the official classification adopted by the American Psychiatric Association are termed paranoid conditions and the paranoid type of dementia precox. However, in cases of this type slight sensorial changes may coexist. Anderson stated that in most such cases the psychosis started with a state of confusion but that as "the confusion abated, a delusional state emerged and dominated the psychic field . . . The dominant feature was the persistence of delusions, often of persecutory type." Ferraro and associates,[44] in a study of the cerebral changes occurring with pernicious anemia, reported that minor diffuse cerebral changes may precipitate paranoid reactions.

43. Meth, H.: Personal communication to the author.

44. Ferraro, A.; Arieti, S., and English, W. H.: Cerebral Changes in the Course of Pernicious Anemia and Their Relationship to Psychic Symptoms, J. Neuropath. & Exper. Neurol. **4**:217-239 (July) 1945.

The cerebral changes presumably do not cause these paranoid syndromes but probably precipitate them or sensitize the patient to them. This occurs not only with pernicious anemia but with other organic conditions, such as early arteriosclerosis. The changes described in cases of pernicious anemia have a vague resemblance to those accompanying cerebral malaria. Associated with both conditions are alterations of nerve cells leading to the ischemic type, numerous small areas of demyelination, proliferations of the capillary endothelium and occasional ringlike hemorrhages.

The importance of malaria in psychoses of the third type is presumably that of a precipitating factor acting on persons whose capacity of resistance is greatly diminished. The prepsychotic personality may determine the schizophrenic or the cyclothymic manifestations of the psychosis.

The fourth class of psychoses consists of organic mental syndromes, often accompanied with focal signs, such as aphasia, and motor disorders. As Huddleson [45] reported, these conditions have no specific characteristics and are indistinguishable from the "psychoses due to disturbance of circulation" such as cerebral embolism, and arteriosclerosis. The pathologic lesions described in cases of pernicious malaria (embolism, hemorrhages, necrotic foci) may well explain the conditions included under this heading.

In addition to these four major types of psychiatric conditions, many authors have reported the occurrence of psychopathic or criminal behavior in patients suffering from malaria, even after apparent recovery. Some patients presented psychopathic behavior accompanied with psychotic symptoms. Alcoholism (Marandon de Montyel [46]), homicide (Anderson,[7] Dowden [47] Arcangelo [48]), incendiarism (Betz [49]) and violence and destructiveness (Cardamatis [50]) have been reported as occurring suddenly not only during the febrile attacks but also as a sequel to malaria. These conditions remind one of "the explosive diathesis" described after head trauma. As a matter of fact, the whole classification of malarial psychoses proposed in this report is somehow similar to the classification of post-traumatic psychoses proposed by Adolf

45. Huddleson, J. H.: Note on Psychoses and Psychoneuroses with Malaria, M. Bull. Vet. Admin. **21**:1-4 (July) 1944.

46. Marandon de Montyel, E.: Contribution à l'étude clinique des rapports de l'impaludisme et de l'alcoolisme, Ann. méd.-psychol. **18**:353-394, 1893.

47. Dowden, cited by Anderson.[7]

48. Arcangelo, S.: Un caso di morte violenta in individuo malarico: Con alcune riflessioni sulla malaria, Comiso, October 1899.

49. Betz, W.: Malaria als oorzak van krankzinnigheid, Geneesk. tijdschr. v. Nederl.-Indië **31**:430, 1911.

50. Cardamatis, J.: Study of Paludisme, Athens, Levin, 1909.

Meyer.[51] This author included with traumatic psychoses a group of post-traumatic deliriums, a second group consisting of psychoses due to a traumatic defect and another group of psychoses in which trauma is merely a contributing factor. One of the most important differences is that paranoid and paranoiac developments seem to be much more frequent with malaria.

The correlation between the psychic sequels and the pathologic process of cerebral malaria has been given special consideration in the present study, in view of its renewed interest in World War II. The evidence would lead one to conclude that whenever a veteran returning from a malarial district shows psychotic or psychopathic manifestations the possibility of malaria as the etiologic factor should be investigated.

SUMMARY

Three cases of cerebral malaria due to infection with P. falciparum were studied. In case 1, in which the most pronounced changes were presented, the infection was so intense that the malarial pigment contained in the blood vessels made the whole angioarchitecture visible in thick, unstained sections. In this case also, numerous small hemorrhages were particularly frequent in the subcortical white matter and in the molecular layer of the cerebellar cortex. The hemorrhages occurred where the circulation was slowed down on account of the large quantity of pigment or where emboli, consisting chiefly of pigment and parasites, endothelial cells and clotted red cells, had completely occluded the vessels.

The red blood cells appeared to extravasate by a process of diapedesis from a vessel located at the center of the hemorrhagic area. They soon disappeared from the center of the hemorrhagic area, giving the false impression that they came from neighboring, collateral capillaries. Subsequently, the red cells disappeared completely, and demyelination occurred in the same area. At the same time, peripheral proliferation of glia took place. Thus nodules were formed, which did not present inflammatory characteristics and should not be called granulomas, as at times they erroneously have been. In case 1 axonal degeneration of ganglion cells was also shown. Other changes, common to all the cases, were proliferation and desquamation of vascular endothelium, acute swelling of and ischemic changes in nerve cells and hypertrophy and hyperplasia of the glia cells.

Though the state of hyperthermia and the toxicosis were considered responsible for some of the changes, the severest pathologic changes were attributed to the mechanical action of the pigment and of the emboli.

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51. Meyer, A.: The Anatomical Facts and Clinical Varieties of Traumatic Insanity, Am. J. Insan. **60**:373-441, 1903-1904.

A review of the literature revealed that psychotic conditions occurring during or after malaria may be divided in four types: (1) acute deliriums, (2) paranoid syndromes, (3) typical psychoses and (4) organic defect syndromes. Psychopathic behavior, with or without psychosis, is also common.

The histologic changes associated with cerebral malaria are considered at times the direct cause of, and at other times only precipitating factors in, the mental syndromes.

It is suggested that when a veteran returning from a malarial district shows psychotic or psychopathic symptoms the possibility of a malarial origin should always be investigated.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

THE EFFECT OF REDUCTION IN NUMBERS OF OMMATIDIA UPON THE BRAIN OF DROSOPHILA MELANOGASTER. MAXWELL E. POWER, J. Exper. Zool. **94**:33 (Oct.) 1943.

Three stocks of Drosophila were established: wild type, different combinations of Bar alleles and eyeless-*2*, which possessed numbers of facets in seven decreasing steps (full eye to total absence of ommatidia). The brains were studied with silver and gold impregnation methods.

The chief characteristic related to reduction in numbers of ommatidia is hypoplasia of the optic glomeruli with the elimination of certain histologic traits of the wild type. The neurologic effects are localized within the optic lobes.

The differentiation and volume of the optic glomeruli are directly correlated with eye size.

Total absence of ommatidia is associated with a reduction of 100 per cent of the external glomerulus, 85.4 per cent of the middle glomerulus, 58.7 per cent of the anterior inner glomerulus and 57.1 per cent of the posterior inner glomerulus.

The extent of glomerular hypoplasia depends on the percentage composition of the ingrowing fibers which have been eliminated.

The volume of the glomeruli is correlated only with the facet number of the adjacent side. The ommatidia-glomerulus relationship is autonomous on each side.

When no fibrillar attachment is established between ommatidia and the brain the optic glomeruli are histologically and volumetrically like those of completely eyeless flies.

The data indicate that the hypoplasia of the glomeruli is not a primary action of the genetic factors but is a secondary result of the ingrowth of a smaller number of centripetal fibers from the genetically reduced peripheral field.

REID, Boston.

AN IRON-ALUM-HEMATOXYLIN STAINING METHOD FOR MYELINATED FIBERS. W. T. NIEMER, J. Neuropath. & Exper. Neurol. **3**:419 (Oct.) 1944.

Niemer describes an iron alum–hematoxylin method for staining myelinated fibers. This method can be used on very old formaldehyde-fixed material and even on old material originally fixed in anticipation of using the Weigert method. A list of reagents (ferric alum, hematoxylin, ammonium hydroxide, sodium borate [borax] and potassium ferricyanide) and the procedure are described.

In sections from non-bichromate-fixed material the gray matter stains light tan to yellow and the white fiber pathways deep blue to black. In sections from bichromate-fixed material the gray matter stains light gray to tan and the white matter deep blue. In both kinds of material color values make the method particularly desirable for photography.

Microscopically, neuron cell bodies are stained yellow, with black nuclei, and red blood cells are stained black. The stain differentiates fine and coarse myelin sheaths and fiber bundles cut in slightly different planes.

GUTTMAN, Philadelphia.

THE MARCHI REACTION: ITS USE ON FROZEN SECTIONS AND ITS TIME LIMIT. P. GLEES, Brain **66**:229, 1943.

Glees describes a modification of Swank and Davenport's method of Marchi staining. Tissues are fixed in solution of formaldehyde U. S. P. (1:4) up to forty-eight hours, washed in 1 per cent potassium chloride for ten minutes and then stained in Marchi solution for about ten days. Frozen sections are then cut and may be counterstained with toluidine blue or light green. According to Glees, preparations treated as he describes show clearly the degenerated fiber tracts and pseudo-Marchi granules are rare.

Glees points out the lack of uniformity of opinion regarding the optimum time for study with the Marchi method after the production of a lesion. In rabbits and cats he believes the optimum time to be at least three weeks. With regard to the length of time in which positive staining can be obtained after the production of a lesion, Glees found time intervals as great as one year for cats and rabbits. The author points out the need for care in interpreting the Marchi reaction in animals subjected to two ablations.

FORSTER, Philadelphia.

Physiology and Biochemistry

ON THE QUANTITATIVE INCIDENCE OF CARBONIC ANHYDRASE IN THE CENTRAL NERVOUS SYSTEM. W. ASHBY, J. Biol. Chem. **155**:671, 1944.

In a previous paper data were presented indicating that in seven species of animals studied, including man, the carbonic anhydrase content of the spinal cord was approximately half that of the cerebrum. The data further indicated that this was not due to any differences in the relative amounts of the gray and the white matter in the samples chosen or to the enzyme accounted for by blood content. The hypothesis was advanced that the greater enzyme content was associated with quantitative metabolic differences between the two areas, which would play a part in establishing their respective functional levels. It was suggested that the enzyme was either in the neurons or in cells accessory to them and that it was either produced in situ or absorbed from the blood corpuscles, which contain it in large amounts. In the latter event, differences in content, perhaps due to differences in circulatory activity, would represent a result of function but might, in turn, modify metabolism differentially. Carbonic anhydrase is found in the central nervous system of various species of animals in patterns which tend to be peculiar to the species. Carbonic anhydrase content has been found to increase progressively rostrally. The enzyme is found in the white matter, in some instances in greater amount in the white matter than in the gray. It is possible that it functions more specifically with reference to the nerve fiber.

PAGE, Cleveland.

THE EFFECT OF INGESTED CHOLINE ON THE TURNOVER OF PLASMA PHOSPHOLIPIDS. H. D. FRIEDLANDER, I. L. CHAIKOFF and C. ENTENMAN, J. Biol. Chem. **158**: 231, 1945.

With the use of labeled phosphorus (P^{32}) it was shown that ingested choline speeds up the rate of phospholipid turnover in the liver. Betaine had a similar action, but its effect was less pronounced than that of choline. As a result of these, and other, observations it was pointed out in 1939 that phospholipid synthesis by the liver is an important intermediary step in the removal and deposition of fat in the liver. The effect of choline on the renewal of phospholipid phosphorus in the plasma was studied in dogs fed a high fat, low protein diet. Radioactive phosphorus was used as the labeling agent. A single feeding of 300 mg. of choline chloride per kilogram of body weight accelerated phospholipid turnover in plasma. Choline increased the rate of change in the specific gravity of phospholipid phosphorus of plasma during the early intervals after the administration of radioactive phosphorus. The maximum values found for the specific activity of phospholipid phosphorus of plasma were higher in dogs fed choline than in those not fed choline.

PAGE, Cleveland.

INTRACENTRAL AND PERIPHERAL FACTORS IN THE DIFFERENTIATION OF MOTOR NEURONS IN TRANSPLANTED LUMBO-SACRAL SPINAL CORDS OF CHICK EMBRYOS. ELMER D. BUEKER, J. Exper. Zool. **93**:99 (June) 1943.

Unilateral extirpations of limb primordia and transplantations of the lumbosacral segments of the spinal cord of 52 to 68 hour chick embryos were made in order to analyze the role of peripheral fields and of longitudinal fiber tracts in the quantitative differentiation of motor neurons in the spinal cord.

After limb extirpations hypoplasia of motor neurons representing a reduction of 75 to 90 per cent occurs. This reduction is even greater in limbless transplants.

A lumbosacral plexus is not formed on the limbless side in transplantation or extirpation experiments.

In several transplants with one well developed limb attached the number of motor neurons was normal on the limb-innervating side.

The results, a growth reduction of 50 per cent in spinal ganglia in the absence of limbs, correspond with the observations of Detwiler and of Hamburger.

The shortening of segments of the spinal cord during development is associated with fusion of ganglia or their approximation. Segments are frequently resorbed from the ends of transplants, and the remaining segments are often incomplete. The motor neurons are affected most seriously, and the median parts are involved less seriously than the sensory column.

Dorsal sensory areas of the gray matter and dorsal and ventral roots are reduced by the removal of limbs.

The author concludes that the development of the lateral motor column of the spinal cord depends on the presence of a developing limb and the pelvic girdle. However, connections with descending fiber tracts are not essential for the development of the lateral motor column of the spinal cord.

REID, Boston.

EXPERIMENTAL HEAD INJURY WITH SPECIAL REFERENCE TO THE MECHANICAL FACTORS IN ACUTE TRAUMA. E. S. GURDJIAN and J. E. WEBSTER, Surg., Gynec. & Obst. **76**:623 (May) 1943.

In the experience of Gurdjian and Webster, the physiologic effects of head injury seemed generally to have been correlated with the intensity of the injury and the pathologic changes produced in the brain. To verify this impression, experiments were undertaken with the dog as the test animal. Morphine anesthesia was used, and the striking force was applied directly to the parieto-occipital bone, the scalp and the masseter muscle having been reflected from the bone. The state of consciousness was determined by the animal's response to pressure applied to the tail and paws.

The experiments were divided into three groups: (1) 30 experiments in which dogs were injured by a falling weight or a hammer blow striking the fixed head; (2) 70 experiments in which the nonfixed head was struck, the hammer, a pendulum and a spring device being used as the injuring force, in about an equal number of experiments, and (3) 38 experiments with injuries of a penetrating type, including gunshot wounds.

Three levels of physiologic response were seen. 1. Minimal: tolerance to the injury, with no significant changes in the blood pressure, respiration or reflexes. all the animals survived. 2. Moderate cessation of respirations or interruption in corneal and palpebral reflexes. All these animals lost consciousness, but most of them were able to survive the injury. 3. Profound: death of the animal during the acute experiment. A remarkable, temporary rise in blood pressure with tachycardia was characteristic.

The skull was practically always fractured, this being necessary for even a moderate effect. It was not possible to produce profound physiologic effects without pathologic damage to the brain, and only in a few instances was unconsciousness produced without associated gross pathologic damage to the brain. Physiologic responses were proportional to the degree of pathologic damage.

Fatalities occurred only if severe cerebral damage had been produced. Consciousness was generally depressed in animals showing minimal response; lost for prolonged periods in animals showing a moderate response and lost until death in animals showing a profound response. Loss of the palpebral and corneal reflexes represented a more profound response to injury than did unconsciousness. A remarkable rise in blood pressure was usually observed after injury in animals showing moderate and profound responses, being prompt and as high as 300 mm. of mercury. The maximum rise was maintained for sixty to one hundred and sixty seconds in the group with moderate responses and for one hundred and eighty seconds in the group with profound responses and gradually fell to zero at the death of the animal. Tachycardia always accompanied this phenomenon. The rise in blood pressure failed to occur if the skull and brain were particularly crushed by the injury or if the spinal cord was transected at the first thoracic level. Removal of both adrenal glands failed to prevent the rise in blood pressure, but yohimbinized animals, which did not respond to epinephrine, showed no increase in the blood pressure after profound injury. The blood flow was decreased in the spleen and increased in the hindpaw, a response which further emphasized the role of the sympathetic nervous system in this post-traumatic type of hypertension.

There was no significant rise in spinal fluid pressure after closed injury to the head. The amount of blood in the spinal fluid was usually commensurate with the intensity of the head injury. Supratentorial gunshot wounds were noted to give intensely increased intracranial pressure at the instant of injury. This was indicated by extension of the cerebellum through a suboccipital craniectomy opening. A gunshot injury 5 cm. below the medulla, with transection of the cord, resulted in contusions of the cerebral cortex.

Penetrating gunshot injuries of the brain resulted in acute physiologic effects, similar to those which were noted with the other forms of trauma.

In these experiments, a velocity range of from 13 to 40 feet (4 to 12 meters) per second was developed. When the head was allowed to move, higher velocities were required to cause a given injury than when the head was fixed. The acute effects of a blow to the head are proportional to the rate of change of the momentum of the striking force. The effects of a cranial trauma are due to a number of factors, which include (1) a sudden increase in the intracranial pressure at the instant of injury; (2) mass movements of the brain, and (3) a diffuse cellular disturbance, due to transmitted energy, with no accompanying increase in intracranial pressure.

SHENKIN, Philadelphia.

STUDIES IN DENERVATION. J. DOUPE and Associates. J. Neurol. & Psychiat. **6**:94 (July-Oct.) 1943.

Methods.—Doupe and his co-workers carried out a number of investigations on patients with lesions of the peripheral nerves. The methods used consisted in measuring the peripheral circulation by means of recording cutaneous temperatures of the finger pads, supplemented in some instances by plethysmographic records of the digits. Various measures to modify the circulation, such as local effects of moderate to extreme cold or heat and injections of epinephrine, were used.

The Circulation in Denervated Digits.—Investigations were carried out to test the validity of the hypothesis of Lewis and Pickering that sympathectomized limbs stay warm while denervated digits become cold. Observations were made on subjects with preganglionic and ganglionic sympathectomies and on subjects with lesions of peripheral nerves. Doupe concluded that, contrary to the results of Lewis and Pickering, the digital vascular reactions are similar in the two groups of patients. The cause of the usually diminished circulation in denervated digits is sensitization to cold produced by degeneration of the sympathetic fibers. This sensitization is made the more manifest by the action of circulating epinephrine,

by the action of vasomotor fibers still supplying the limb and by variations in local and general blood pressure. Part of the difference in the state of denervated and ganglionectomized digits may be ascribed to the persistence in the latter of some postganglionic fibers. The reactive hyperemia which has been observed in denervated digits is in part mediated by arteriovenous anastomoses, is not dependent on any neural mechanism, is greatly slowed by a high sympathetic vasoconstrictor tone and is not affected by the vasoconstriction caused by cooling the denervated digit. Denervated blood vessels appear to be histologically normal. There is no correlation between Raynaud's syndrome and sensitivity associated with denervation. In the former condition there is no hypersensitivity to epinephrine. In the latter there is no history suggestive of vasospasms, the cyanosis is slight and there is a ready response to reactive hyperemia. Thus, with lesions of peripheral nerves the blood flow is adequate to the needs of the tissue, while with Raynaud's syndrome ischemia occurs. The trophic changes in denervated digits are attributed to the lowered tissue metabolism consequent on the persistent coldness, since the blood supply is adequate. The sensitivity to cold in denervated digits may be explained on the basis of changes in hydrogen ion concentration, since a fall of temperature would directly raise the p_H and produce vasoconstriction, or decrease the formation of acid metabolites and thus indirectly lead to elevation of the p_H and vasoconstriction. The regain of tone following denervation is ascribed to the action of local influences on sensitized vessels. A circulating vasoconstrictor substance in the blood may only be assumed in the case of systemic disorders.

Inflammation and Trophic Ulcers in Denervated Areas.—Slow healing of trophic ulcers, produced by burns or pressure, in denervated digits has been ascribed to diminished blood supply. Since the authors contend, however, that the blood supply of denervated digits is adequate, there must be other causes for the delayed healing. In the case of ulcers following burn, the slow healing is only apparent, since data are lacking on the extent of the original trauma because of loss of pain sensation in the denervated area. In the case of ulcers produced by pressure slow healing is due to edema associated with impairment of the lymph drainage in the extremity. The occasional presence of a vesicular eruption in cases of peripheral nerve lesions also is due not to denervation but to a variety of cheiropompholyx.

Mechanism of Axonal Vasodilation.—On the basis of a case of section of the ulnar nerve, Doupe concludes that axonal vasodilation is mediated by fibers other than those associated with sensation. The mechanism of axonal vasodilation is still obscure. According to Lewis, it depends on efferent cholinergic fibers having their trophic center in the posterior root ganglia and distributed in the skin in the form of a plexus, stimulation of which releases the so-called H substance. A review of the literature fails to corroborate this view. The authors offer an alternate hypothesis, viz., that the fibers subserving axonal vasodilation are afferent and that they terminate in a branching axon system with receptors specially sensitive to products of tissue damage, similar to histamine. Axonal vasodilation is thus attributed to the metabolites of nerve fibers, rather than of cells of the skin.

Epinephrine.—Denervation of digital vessels in human subjects renders them hypersensitive to the vasoconstricting action of epinephrine. This is due to degeneration of sympathetic fibers, which produces in the vessels of denervated digits a lowered threshold and a prolonged response to the action of epinephrine. The vessels of preganglionectomized digits, on the other hand, show only a lowered threshold. This difference between degenerative and nondegenerative section of sympathetic nerves is due to a loss of "accommodation" in the former which is not present in the latter. Emotional stimuli cause a release of epinephrine in the body, but the need for heat conservation is a more variable and less constant cause of such liberation. Thus, the original view of Cannon that secretion of epinephrine is associated with mental excitement is more correct than his later

assumption that epinephrine participates in many of the ceaseless variations in body function. Peripheral neurogenic vasoconstriction is not necessarily accompanied with the release of epinephrine, an indication that within the sympathetico-adrenal system different patterns of behavior are elicited by stimuli of different types. Epinephrine could be liberated in the body in amounts comparable to the rapid intravenous injection of 2 micrograms or to injection of the drug for longer periods at the rate of 6 micrograms per minute. In other circumstances, much larger amounts might be liberated, which would suffice to initiate persistent vasoconstriction in a denervated digit.

Circulation in the Skin of the Proximal Parts of the Limbs.—Doupe and his collaborators confirmed the view expressed by Grant and Holling that there exists a vasodilator sympathetic supply to the blood vessels in the skin of the proximal parts of the limbs by producing active vasodilation in response to intense heating of the body. The lack of effect of nerve block when the subjects are cold shows that there is no significant vasoconstrictor innervation of the vessels in these areas of the skin. The vasodilation is not dependent on the activity of the sweat glands, since the action of the latter can be abolished by atropine without thereby decreasing the vasodilation. The thesis of Grant and Holling is not refuted by the occurrence of vasodilation following sympathectomy. The latter phenomenon may be due to discharges in vasodilator fibers, which are decentralized by the operation, to the anesthetic and to absorption from traumatized tissues.

Sebaceous Secretion.—The author and his co-workers estimated the sebaceous secretion in a subject with a sympathectomy and in another subject with a lesion of the brachial plexus. They found that the sebaceous glands can function in the absence of all nerve fibers. Similarly, the growth of hairs and the metaplasia of the cells of the epidermis are unaffected by deprivation of direct nerve influences. Sebaceous secretion is thus simply a manifestation of the growth of the cells of the sebaceous glands. The physical state of the skin influences the production and absorption of the sebaceous material. The abundant secretion in cases of lethargic encephalitis may be due to disturbances in hormonal regulation.

Effect of Electrical Stimulation on the Circulation and Recovery of Denervated Muscle.—The value of electrical treatment of denervated muscles was investigated in a series of 12 patients after suture of the musculospiral or the posterior interosseous nerves. It was found that electrical treatment had no beneficial effects on the return of motor power. This failure was ascribed to the fact that the treatment does not impose a strain on the muscles of sufficient intensity to be of therapeutic value. The amount of electrically induced exercise was estimated by using the rate of blood flow as an index, and it was found that even more intensive stimulation produced a relatively slight increase in blood flow. The only benefit derived from electrical therapy is in induction and reeducation of muscular movements.

Contractility and Excitability of Denervated Muscle.—The electrical reactions of denervated muscles consist in changes in contractility and excitability. Repetitive excitation is likely to develop in denervated muscle when it is subjected to an electric current. This phenomenon is a persistence of potentials throughout the phase of muscle shortening, due to the fact that each muscle fiber is responding more than once. It is readily produced by a constant current. The phenomenon of galvanotonus is also attributed to the repetitive firing of the muscle fibers. Denervated muscles usually show prolonged contraction, which is due to repetitive stimulation by constant currents in conjunction with a cool state of the muscle. Similarly, denervated muscles show prolonged excitation, which is also due to repetitive stimulation plus the relation of the muscle fibers to the field of the current. Electrical reactions are of clinical value only when positive, for when negative they may be attributed to factors other than the state of degeneration of the muscles.

MALAMUD, San Francisco.

Neuropathology

THE EFFECTS OF IODIZED POPPYSEED OIL AND IODINE-CHLORINE IN PEANUT OIL IN THE SUBARACHNOID SPACE OF ANIMALS. EDWIN BOLDREY and ROBERT B. AIRD, J. Nerv. & Ment. Dis. **99**:521 (May) 1944.

After the fall of France, in 1941, the authors undertook to find a satisfactory substitute for 40 per cent iodized poppyseed oil, which was no longer available. For this purpose, 27 per cent iodine and 7.5 per cent chlorine in peanut oil (Iodochlorol) was selected and was tested for comparison with 40 per cent iodized poppyseed oil. In a group of dogs, 2 cc. of the radiopaque substance was injected into the subarachnoid space through the cisterna magna. Four dogs received an additonal injection after a week's interval, and another group of 4 dogs received 2 cc. of oil plus 2 cc. of the animal's own freshly drawn blood. On 2 animals which had received the Iodochlorol and on 1 which had been given an injection of iodized poppyseed oil autopsies were performed on the fourth or fifth day. Mild subarachnoidal and adventitial inflammatory changes were noted in the cervical region in all the dogs. Two dogs, followed for eighty-six days after the injection of iodine and chlorine in peanut oil, showed a transient rise in the spinal fluid of polymorphonuclear leukocytes and lymphocytes, and autopsy showed definite gross adhesions in the upper cervical region and numerous thick-walled cysts about the brain stem. In a similar experiment, in which 2 dogs received iodized poppyseed oil, the transient rise in the cell count was higher in each instance, and the pathologic changes were more extensive and severe. Animals which had received two injections of either iodized poppyseed oil or the iodine-chlorine preparation showed a more pronounced reaction than those which had had only one injection; this was especially true if a relatively long time was allowed to elapse after the second injection before the dog was killed. In other animals, the addition of blood to the injected oil materially increased the irritating effect.

The most significant observation was the progressive chronic adhesive reaction found after three months in animals given injections of either of the oils. Although the reaction with the iodine-chlorine preparation was slightly less than that with the iodized poppyseed oil, there was sufficient reaction in either case to make the removal of the oils from the subarachnoid space desirable.

CHODOFF, Langley Field, Va.

VASCULAR CHANGES IN EXPERIMENTAL ANAPHYLAXIS OF THE BRAIN. A. FERRARO, J. Neuropath. & Exper. Neurol. **4**:1 (Jan.) 1945.

Ferraro reports observations on the brains of monkeys which were subjected, over varying lengths of time, to parenteral injections of egg white. Histologic study revealed that if an animal died soon (fifteen hours) after an intracerebral injection typical features of the Arthus phenomenon, with necrosis, hemorrhages, edema and perivascular reaction, consisting mainly of the presence of polymorphonuclear leukocytes, were seen. In an animal which survived six days after the last intracerebral injection of antigen the perivascular reaction showed a mixture of polymorphonuclear leukocytes and lymphocytes. In other monkeys in which the injection of antigen was prolonged for a much greater period the perivascular reaction was characterized by the presence of lymphocytes associated with large mononuclear cells. The longer the period of sensitization, the more dominant was the lymphocytic-histiocytic type of reaction. In addition, the formation of giant cells, derived either from large mononuclear cells or from histiocytes, became an added important histologic feature. The presence of the typical Arthus phenomenon was therefore not essential in determining the anaphylactic origin of a pathologic process.

In another series of experiments in which the antigen was administered intramuscularly, some of the animals were given injections for a long period without presenting clinical symptoms of involvement of the central nervous system, whereas

under identical conditions other animals died after a number of injections, which varied from 29 to 103. The sensitization of the animal took a minimum of one hundred and twelve days and a maximum of four hundred and five days, and the histologic changes were similar to those seen in the later stages of experimental anaphylaxis, namely, the lymphocytic-histiocytic type accompanied with varying degrees of parenchymatous change, ranging from minimal alteration to necrosis. The necrosis was independent of the hemorrhages with which it was associated in the acute stage of the reaction.

GUTTMAN, Philadelphia.

A CASE OF PERIARTERITIS NODOSA WITH DECEREBRATE RIGIDITY AND EXTENSIVE ENCEPHALOMALACIA IN A FIVE YEAR OLD CHILD. N. MALAMUD, J. Neuropath. & Exper. Neurol. **4**:88 (Jan.) 1945.

Malamud reports the case of a 5 year old boy who, while convalescing from an infection of the upper respiratory tract, had fleeting pains in the joints and abdomen. Examination revealed a systolic cardiac murmur, elevated temperature and leukocytosis but no swelling or redness of the joints. Acute rheumatic fever was suspected. One week later the symptoms began to subside, but the patient suddenly had a series of seizures, became comatose and exhibited decerebrate rigidity. Tendon reflexes could not be elicited, and there were no signs of involvement of the pyramidal tract. The pupils were dilated and fixed to light, and there was mild papilledema. Lumbar puncture and studies of the cerebrospinal fluid revealed nothing significant. Ventriculographic studies suggested the presence of a tumor of the brain stem. The patient died about two and a half months after the onset of his illness.

There was massive necrosis of the cerebrum, while the brain stem and cerebellum were of normal consistency and the basal vessels were soft and delicate. Microscopic observation revealed complete destruction of the cytoarchitecture, with few or no nerve cells remaining, and the brain tissue was replaced with vacuoles of varying sizes or with amorphous masses of precipitate. Within the necrotic tissue a very active mixed mesenchymal and glial reaction occurred. There were marked proliferation of microglia and an equally intense proliferation of reticulin fibers, with newly formed blood vessels. The neuroglial reaction was moderate. In the leptomeninges there were a few polyblasts and lymphocytes. The white matter showed intense, but more patchy, involvement. Extensive necrotic changes were also found throughout the optic chiasm, the caudate nucleus, the putamen and the globus pallidus. The thalamus, with the exception of the centromedian and intralaminar nuclei, was destroyed, partly as the result of secondary degeneration. The hypothalamus and the subthalamus were only slightly involved. The necrosis terminated at the level of the red nucleus. The brain stem and the spinal cord exhibited only mild secondary degeneration of the pyramidal tracts. The cerebellum, however, showed pronounced diffuse degeneration of nerve cells in the Purkinje layer and the dentate nucleus. Study of the meningeal and cerebral blood vessels revealed lesions in a subacute phase of hyalin necrosis of the subintima and media, perivascular infiltration with lymphocytes and fibroblastic proliferation of adventitia and intima, encroaching on the lumen. Similar vascular lesions were found in the heart, and somewhat more chronic ones were noted in the walls of the trachea, the esophagus and the gastrointestinal tract and in the kidneys.

Anatomically, there was a conspicuous discrepancy between the extensive destruction of the cerebral parenchyma and the restricted vascular lesions. The discrepancy between the involvement of the parenchyma and that of the vascular system may be of significance in understanding the nature of the disease. Malamud states that the onset following an infection of the upper respiratory tract and its initial general effect on various organs, followed by an intense necrotizing process in the brain, clearly out of proportion to the extent of the arteritis, suggests an allergic reaction.

GUTTMAN, Philadelphia.

Psychiatry and Psychopathology

PSYCHOSES OCCURRING IN SOLDIERS DURING THE TRAINING PERIOD. MARGARET HITSCHMAN and ZULEIKA YARRELL, Am. J. Psychiat. **100**:301 (Nov.) 1943.

Hitschman and Yarrell studied 100 soldiers who were admitted to the psychiatric division of Bellevue Hospital. One third had enlisted; the remainder were drafted. Only 1 had seen actual combat. The distribution of diagnoses was as follows: schizophrenia, 78; manic-depressive psychosis, 8; psychopathic personality, 6; psychoneurosis, 4; mental deficiency, 1; epilepsy, 2, and syphilis of the central nervous system, 2. Thirty-one of the 100 men had had previous psychiatric treatment. In correlating the length of service with the onset of the illness, the authors found that 70 of the group became ill within five months of entering service. On reviewing the preinduction histories, the authors found that 38 had made good adjustments. Twenty-three of the 100 men became ill within the first two weeks of service, and in this group the authors felt that military service played a role as a precipitating factor. In a comparison of the clinical features of the psychoses found in these soldiers with those in a group of civilians of similar age and sex, no significant difference was apparent. In order to lower the incidence of psychiatric casualties, the authors recommend social investigations to eliminate men with previous admissions to mental disease hospitals, investigation of police and social agency records, a three months' probationary preinduction period, special training units in replacement centers and psychiatric examination of maladjusted soldiers after three months.

FORSTER, Philadelphia.

CLINICAL AND EEG STUDIES IN OBSESSIVE-COMPULSIVE STATES. B. L. PACELLA, P. POLATIN and S. H. NAGLER, Am. J. Psychiat. **100**:830 (May) 1944.

Pacella, Polatin and Nagler studied the electroencephalograms of 31 patients with obsessive-compulsive states. Twenty-six of these patients were classified as psychoneurotic, and 2 of them had petit mal attacks in addition to their obsessive-compulsive state. Five patients had schizophrenia. Twenty of the 31 patients had abnormal electroencephalograms, 14 of whom presented occasional or frequent runs of 2 to 4 per second, high voltage activity. In most records the paroxysmal disturbance was apparent only after hyperventilation. Only 9 of the 31 patients had definitely normal records. The patients under 30 years of age had a greater incidence of abnormalities in the electroencephalogram. There was some indication of a higher incidence of a family history of psychopathy in the group with abnormal electroencephalograms, but the authors conclude that the differences, while suggestive, are not statistically significant. The severity of the clinical symptoms could not be correlated with the electroencephalographic pattern.

FORSTER, Philadelphia.

A RUNAWAY FROM HOME. HUGO STAUB, Psychoanalyt. Quart. **12**:1, 1943.

Although many elements participate in the production of a criminal, among which are economic and social factors, traditions, the level and form of civilization, politics, power and psychologic factors, Staub doubts whether there is a genuine criminal who is not one because of an inner conflict, i. e., anxiety feelings, feelings of guilt or a need for punishment. Reality often replaces the inner mechanisms of guilt and self punishment by pressing hard enough and by inflicting sufficient suffering to weaken the inner restrictions and relieve the inner anxiety, thus releasing the aggressive tensions. The author believes that in all criminals there is an emotional urge to act dissocially, which originates in an unconscious conflict. In prison a criminal may be calm and well adjusted, but when he is released he becomes shaky, disintegrated, unbalanced, inhibited and emotional except when committing a crime. The interplay between the reactions of society and the criminal's acting out of his unconscious fantasies of self punishment result in the

development of a criminal character in the latter. In proof of his thesis, Staub offers the analysis of a 17 year old boy who showed a compulsive tendency to run away.

The author emphasizes two points in discussing the case.

1. Running away is behavior which is in contradiction to the tendency of a child to cling to infantile dependencies. The child may run away because he is being treated badly in his home, or he may run away, as in the case cited, because he has feelings of guilt about his unconscious murderous and incestuous impulses. With the latter motive there are associated some pleasure gains—by running away the child can make his mother cry for him and want him back; he can take revenge on her, and he can imitate his father by appearing capable and self reliant.

2. In treating patients whose behavior is antisocial, it is necessary to modify the usual psychoanalytic procedure. Such patients are at first absolutely passive in treatment because they have strong feelings of frustration and disappointment to which they react by obstinacy. The analyst must be active in convincing the patient of his willingness and ability to help and of his perception of the patient's inner problems. The patient will test the analyst by every means possible to see whether he means what he says. If the patient is a braggart, he must be shown that his exaggerated self confidence is an overreaction to his feeling of helplessness. He must be helped to lose his anxiety about his helplessness by his confidence that the analyst will stand behind him. With the adolescent, the analyst must appeal to his intelligence. The analyst's activity in this preparatory period is directed toward gaining the patient's confidence in order to establish a strong positive transference, to draw off the excess of anxiety and fortify the badly damaged self confidence and to permit the controlling and restraining forces of the ego to operate. This accomplished, the usual technic of psychoanalysis is employed.

PEARSON, Philadelphia.

Society Transactions

PHILADELPHIA PSYCHIATRIC SOCIETY

O. Spurgeon English, M.D., *Presiding*

Regular Meeting, March 9, 1945

Modern Concepts of the Convulsive State. Dr. Temple Fay.

The use of insulin, metrazol and electric shock has made the convulsive seizure such a commonplace event that the psychiatrist and the public as well have abandoned the concept that such attacks are evidence of mental inferiority and degeneration. With this remarkable change in concept there is a recurrence of many challenging questions.

The concept that the convulsive seizure may be a latent pattern of an early evolutionary type of reaction pattern, at approximately the level of the amphibian, seems worthy of consideration in view of the fact that the pattern of movement never includes the acquired skilled activity and the coordinated types of action patterns seen in the forms above the mammalian level.

Many circumstances surrounding a seizure cannot be harmonized with the concept of an "irritative" or a "stimulative or overflow" response. The latent period existing between the application of a stimulus to the brain organ and its response in terms of a typical convulsive seizure has not received the attention or consideration it should. Stimuli applied to peripheral nerve roots or to the cord itself yield an immediate and violent response.

Instead of electric shock stimulation being the cause of the motor discharge, the latent interval may well be concerned with the effects of stunning or removing the inhibitory influence of the cortex so as to permit spontaneous release of lower levels of motor activity similar to the early phylogenetic pattern.

The former concept of a convulsive seizure being "an evil discharge of purposeless movements" has given way to a more rational consideration of the removal of higher evolutionary dominance in terms of motor patterns and cerebral levels, rather than of direct "irritation or discharge of cortical energy" from pathologic areas adjacent to the motor cortex.

Drawings of a Seven Year Old Child. Dr. Robert S. Bookhammer.

Drawings by a 7 year old girl depicted a boy having his genitals cut off by a large knife in the presence of little girls, who were making fun of the situation. The child was reported to be quite a tomboy, definitely regretting that she was a girl. The drawings were viewed as an attempt to resolve her conflicts in relation to this envy, thus enabling her to become more accepting of her femininity. They were offered as an addition to the ever increasing data supporting the theories related to the little girl's concern with her lack of a penis. It was emphasized that this child was in normal health and occupied with the normal problems of her psychologic development.

DISCUSSION

Dr. Gerald H. J. Pearson: All of us who do any type of psychotherapy are always glad to have objective evidence from children which bears out some of the inferences we draw of what goes on in the subconscious mind of the adult patient. It is always good to have objective material that will show these conflicts as they develop and the way in which the child learns to handle them.

It is important that these drawings came from a normal child. One sees many drawings like this in psychiatric work with sick children. There is no question that the drawings show that this little girl is having a hard time reconciling

herself to the fact that there are creatures in the world who are not the same as she is.

The father picked these drawings out of the wastebasket, where the child had thrown them. At the same time, he noticed that the child seemed to be a little upset in relation to her brother. Perhaps many parents would have spanked this little girl and said that she was naughty. When a parent is able to get material produced by the child showing that the child is having an emotional problem, they could do something to help the child during this period. Emphasis should here be put on the fact that it is "just as important to be a girl as a boy."

DR. JOSEPH C. YASKIN: Did Dr. Bookhammer say this child was 7 years of age when these drawing were made? How reasonably certain is he that she really is well?

DR. HAROLD D. PALMER: What criterion does one use in saying "a perfectly normal little girl"? This child had anxiety, a great deal of anxiety. She put the drawings where they would be found. She put them there with the intention of punishment. A child of 7 is clever enough to have disposed of them, and she would not have put them where they would have been discovered by the parents if she had not wanted them to be found.

DR. O. SPURGEON ENGLISH: That there is an inherent tendency toward destruction in human beings, whether male or female, is here shown pretty clearly. Freud spoke of the death instinct, and Menninger developed it further in "Man Against Himself" and showed how many different forms this instinct takes in human beings.

One sees so much envy and jealousy, criticism and destruction in the world. It is very common. A woman will envy another woman her appearance, another her good looks and another her ability and talents in some field and can feel only unhappy about it and want to criticize her. Men envy each other their physical prowess and ability, instead of emulating each other.

Such aggressive and destructive trends show how much help children need in early life, how much attention one needs to pay to satisfying sexual education.

Whatever one's opinion may be about the castration complex as a theory, one will surely agree that children need a great deal of help and direction in how to accept themselves as they are. They need much help and proper direction of such destructive tendencies as are shown in this child, whether she is regarded as sick or normal.

DR. ROBERT S. BOOKHAMMER: I purposely made this communication short and did not go into a considerable history of this child. If I had gone into it more deeply, perhaps some of these questions would have been anticipated and answered.

Dr. Yaskin will have to take on faith my statement that she is well. I have known this little girl fairly well over a period of years. She is perhaps in the upper third of her class in school and is very popular with the other children. She presents no behavior problem, either in or out of the home. She is happy and contented. She shows no particular phobias or obsessions or anxieties beyond the usual range of childhood.

In answer to Dr. Palmer's question: This child has been perhaps a little more fortunate than most in growing up in a household where there has never been much restriction of any sort on expression. Since she has been able to draw, she has drawn pictures of animals, in which she includes the genitalia of the animals and draws only male animals, never females.

I suppose every 7 year old girl has a certain amount of anxiety, and this child's need to express her problems in these terms indicates that she has anxiety. I do not think that such anxiety in a 7 year old girl is necessarily pathologic. Every little girl has this kind of anxiety, which she has to work out in some way or other, and this seems a pretty good way of doing it.

Utilization of a Therapy Group in Teaching Psychotherapy. Dr. Samuel B. Hadden.

Four years ago students and interns interested in psychiatry began attending sessions of the psychotherapy group at the Philadelphia General Hospital, and in the fall of 1944, 15 students, volunteers, were selected to work with men discharged from the services for psychoneurotic disabilities or rejected for service for the same cause.

Each student is assigned a new patient, takes the history, carries out the indicated examinations and usually arranges a weekly conference other than the interview at the group discussion. After twenty to forty minutes spent in personal interview between patient and student, both gather with the leader for group discussion. New patients are admitted at any time, giving opportunity for repetition of essential principles, such as repression, sublimation, projection and introjection. The patients understand the sessions are part of the teaching of the students and accept their student-doctors confidently. At times the students are assigned topics which they present to the group and which are the subject of discussion by both patients and students.

The purpose of the course was to give students an appreciation of the psychotherapeutic procedures, and the students have reported that they have acquired an understanding of themselves as well and that their personalities have been favorably affected. They have unanimously stated that this was the first opportunity they had had of working with psychiatric patients on an intimate basis. Many expressed surprise that the symptoms of neurotic patients were accepted as being real and that such symptoms as tachycardia, epigastric pain and digestive disturbances could be influenced by psychotherapy. At first they regarded with skepticism the assurance of improvement in patients without medication. The students felt that at least two, or even three, sessions a week were in order.

DISCUSSION

Dr. Robert A. Matthews: For the past twenty years there has been a gradual and, I should say, satisfying improvement in the teaching of psychiatry all over the country, especially in the better medical schools. It can be best presented didactically through student clinics and with student work in the wards.

My associates and I are still trying to find a way to present adequately the problems of the psychoneuroses and the psychosomatic problems. We have tried a lecture form, and I am fairly convinced that we did not succeed very well in presenting didactically material regarding the understanding and treatment of the psychosomatic patient.

We have tried the presentation of psychoneurotic patients before large groups of students. At one time I thought this method was not feasible, but the more I see of it the more I believe that one can present psychoneurotic patients to large groups of students, actually discussing the patient's problem before a student group. However, that still does not solve the problem of allowing the student to get the feel of the psychoneurotic problem.

Dr. Hadden has shown one of the ways in which one may be able to do this. Students, in this plan, are allowed to talk to individual patients. Then the group gather together, and certain basic principles are discussed and the patients are encouraged to discuss their own problems. This permits a combined individual and group interview, which, I think, is excellent. The trouble is that at present there are not enough psychiatrists to guide the students in their individual interviews. I think Dr. Hadden has presented something that is really stimulating. Medical schools cannot consciously continue to send students out so poorly prepared in this most important of all subjects.

One must be careful that one does not make psychotherapy seem too easy to the student. A certain type of patient who applies at this sort of clinic may not represent the entire cross section of the psychoneurotic problem, and we may be a little careless, if we do not watch ourselves, in not giving the student a healthy respect for the difficulties in this type of treatment. This facile handling of the problem is illustrated in "Lady in the Dark," in which, after four or five sessions, the conflict seems unearthed and the patient married the man of her choice, gets better and lives happily ever after. The student must not think that he will get to the deeper layers of the personality in such group meetings, as can be done only through individual interviews, in many cases extending over long periods. Dr. Hadden is to be congratulated in his untiring efforts.

DR. JOSEPH C. YASKIN: It is not necessary to comment on the value of Dr. Hadden's paper. That is self evident.

It might be of interest to look back and see why such methods were not available years ago. I believe that the answer is to be found in the fact that the teachers of a generation ago did not know much about the psychoneuroses and could not teach them. I believe that they would teach the neuroses very sensibly by reason of their personal insight, but they did not have any semblance of a systematic approach.

If a patient has a cerebral tumor or gallstones, he calls a surgeon, whereas the general practitioner has to handle the psychoneuroses. Therefore, he should be better able to manage them.

DR. ISADORE RODIS, Washington, D. C.: Dr. Hadden has established a precedent. The psychiatrist is coming out of his ivory tower and getting in contact with the students.

At Georgetown University the students are appreciative of the fact that they can see the psychiatrist and can talk with him. My colleagues and I have found this valuable in the outpatient department and in conferences held by the department of medicine, in which the department of psychiatry has been invited to participate and in which the sessions have been so arranged by the department of medicine that the patient with a psychosomatic disorder is presented to the section of students by the students themselves.

DR. GEORGE D. GAMMON: The reaction of various departments of the hospital to this plan of group psychotherapy has been rather interesting. In some departments there were physicians who were enthusiastic about referring patients, for instance, the clinic for gastrointestinal diseases, which abounds in such problems. Certain other departments, where elixir of phenobarbital flows freely, have refused to give up their patients. Dr. Hadden decided to undertake the treatment of a group for veterans which would meet at night. In order to get assistance for that, it was decided that the senior medical students would have to be called on to help out. They have been enthusiastic and faithful in attending. They are sincerely interested in trying to learn more about psychiatric problems and problems of mental behavior.

There is great interest in this type of treatment not only among medical students but among other people. Many other persons have asked whether they could attend some of these classes. That merely foreshadows Dr. Yaskin's proposal to teach the principles of psychiatry in general education.

DR. LOUIS H. TWYEFFORT: Dr. Hadden is proving to the future generation of medical practitioners the reality of psychosomatic factors. I should like to put in a plea for the use of such adjuvant methods of teaching as motion pictures in emphasizing the role played by emotional factors in many disturbed physiologic states. Such moving pictures could be put to good use in future teaching programs to make the coming physician aware of the physiologic reality of emotional factors, thus gradually overcoming the far too current concept that most psychosomatic symptoms are but figments of the imagination.

O. Spurgeon English, M.D., *Presiding*

Regular Meeting, April 13, 1945

The Mentally Diseased Patient as an Individual. DR. GEORGE S. SPRAGUE.

The stimulus for this paper was found in Freud's "Mourning and Melancholia," in which he said: "Both scientifically and therapeutically, it would be fruitless to contradict the patient who brings these accusations against himself. He must surely be right in some way and be describing something that corresponds to what he thinks."

There are dangers involved in dealing with the psychiatric patient on the basis of diagnosis instead of insisting on learning his individual attitudes, reactions and symptoms. Generalizing, like a composite photograph, allows individual items to be lost sight of, to the detriment of the best management and understanding of the patient. Each person wants to be considered as an individual and is correct in prizing his personal differences. No matter what his symptoms, there are contained in them clues to a relationship of cause and effect which should be used to his advantage. The symptom is not the problem but, rather, the evidence that problems exist and should be sought out. But while psychiatry is interested as never before in subjective material, application of such progressive attitudes even yet lags behind awakening knowledge.

No two people are likely to build identical concepts for any of the familiar notions, such as death, love and politics; and if effort is not individually applied the patient may unwittingly be importantly misjudged and misunderstood. The result is a lowered effectiveness of therapy and a scientific loss in comprehension of the problems. In the period of postwar readjustments the challenge will be particularly urgent because of the numbers of returned service men who have difficulties in settling into the old situations and culture, while at the same time they have learned in service to look to psychiatry for help as never before.

DISCUSSION

DR. ELEANOR KOCH: I wish to express my appreciation of this paper and to welcome Dr. Sprague to his practice of psychiatry in Philadelphia.

The emphasis which he places on the consideration of the patient as an individual is one which psychiatrists tend to take for granted as an "ABC" in practice. It is certainly that; but, although it is an emphasis to which they give ready lip service, a working use of all that is suggested in this paper requires continued and purposeful reiteration in its application to the practice of psychiatry.

I have thought of reasons for the difficulties the psychiatrist encounters in his attempts to individualize each patient's problems. Much of this tendency to categorize is related to the security value for the psychiatrist in the classified approach to a subject's difficulties. That his own sense of security should be obtained at the patient's expense is not compatible with good psychiatric practice.

DR. PHILIP Q. ROCHE: I wish to express a word in praise of Dr. Sprague for his stimulating paper and to convey to him a special word of appreciation for his directing our attention to the neglected field of criminal psychiatry. In this connection, Dr. Sprague's comments on the uncritical use of rigid, diagnostic labels find particular application in dealing with patients whose behavior is disquieting. The tendency to regard people as diagnostic entities rather than as living persons is nowhere more persistent than in the treatment of delinquents. This is exemplified in the creation of figments of what people are fancied to be and in attempts afterward to squeeze them into such predetermined shapes. There come to mind such diagnostic terms as "defective delinquent," "moral imbecile," "psychopathic personality" and "constitutional psychopathic inferior."

I doubt the real usefulness of such terms in service to scientific aims. Some say they have value in the immediate practical expedients of penology, but

psychiatrists should always treat them with suspicion and be mindful of their corruptive effect. This is demonstrated too often in the use of these terms, which lend themselves to semantic distortion, to convey more of name calling than of understanding. Worse still, such terms creep into the law and petrify into sacred anachronisms. Such is the case of the present law, which has created a subspecies of monster called "defective delinquent." This brings to mind the admonition of Montaigne, "Through presumption they make laws for nature and marvel at the way nature ignores those laws."

DR. SEYMOUR DEWITT LUDLUM: I am always intrigued by the fact that nobody ever raises the question of constitutional basis, that is, the physiologic constitutional basis.

DR. GEORGE S. SPRAGUE: I appreciate the discussions of this subject. A statement made by Dr. Roche seems especially in point—that semantic problems are such a large part of this matter. An incident which will serve to illustrate this point occurred when a boyhood chum of mine was invited to spend a week on a friend's farm, where the friend had been contentedly spending the summer. But when the visitor came indoors with the remark: "Did you know that there is a quadruped on this farm?" the boy who lived there was for some while afraid to go outdoors any more. In a similar fashion, psychiatrists are all prone to deal quite too predominantly with terms, rather than with the true facts about the patients and their problems.

Narcosynthesis of the Civilian Neurosis. DR. HERBERT FREED.

With the aim of shortening psychotherapy in selected cases of neurosis, a technic somewhat similar to that which Grinker and Spiegel called narcosynthesis was utilized. The dynamic principle involved was that of mobilizing affects so that the emotional life of the patient would be reintegrated by fusing the idea with the feeling. It was felt that the barbiturates had a more or less specific effect not only in allaying anxiety but also in producing an affective state which allowed for a freer expression of erotic and aggressive drives. These could be utilized by the therapeutist in connection with the repressed memories and phantasies frequently obtained, as well as with previously known data.

Twelve patients were treated, of whom 4 had formal psychoanalytic therapy for periods up to a year and the others less intensive psychotherapy. Almost all the patients showed affective deviations prior to narcosynthesis, and their condition was described as schizoid, compulsive or detached.

The paper was a preliminary report. The patients had received from two to twelve treatments with narcosynthesis. The responses of the majority were considered promising.

DISCUSSION

DR. LOUIS H. TWYEFFORT: Various workers giving barbiturates intravenously in narcosynthesis report the occasional occurrence of pulmonary edema, regardless of the quantity of drug used and sometimes in spite of the patients having reacted quite normally during previous treatments. The injection of atropine prior to treatment has been advised. What has been Dr. Freed's experience in this respect?

In what little experience I have had with narcosynthesis I have been impressed with the way in which it facilitates the expression of repressed aggression, which in many instances seems to be the chief determinant of the patient's anxiety.

DR. HERBERT H. HERSKOVITZ: I should like to call the society's attention to the fact that Dr. Freed was one of the first to report results of insulin and metrazol shock therapy to this society. He is now the first to report on a method which is destined to become generally used in psychotherapy. Psychiatrists are always on the lookout for methods with which to shorten psychotherapy. However, one must be sure not to confuse a means with an end, a method with a therapy. Barbiturates serve no purpose other than to lessen repression, to bring

forth repressed memories and affects. Many would-be psychotherapeutists will, if this fact is not sufficiently understood, talk glibly of giving "sodium amytal treatments" or "sodium pentothal treatments." The barbiturates themselves have no therapeutic effect. They merely weaken repression and thus are an aid to psychotherapy. I should like to stress my conviction that therapeutic success is due not to the drug but to the therapeutist. I do not think the barbiturates produce a state of euphoria any more than alcohol or other drugs can produce aggression or euphoria. By lessening inhibition, by weakening repression, the patient's underlying tendencies are brought out. I cannot believe that there is a definite chemical reaction on certain areas of the brain produced by the barbiturates which causes a feeding of well-being. I wonder whether the feeling of well-being, described by Dr. Freed and others, is not caused by a release of tension and by the allaying of anxiety.

One hears more and more of treatments such as narcohypnosis, narcosynthesis, narcoanalysis and others. I hope that with the intravenous administration of barbiturates there will not be built up a confusing array of terms, all of which mean the same thing, psychotherapy.

DR. H. CRAIG BELL: Dr. Freed's presentation has definite psychotherapeutic value in a limited field. I should like to ask him two questions: How long does he find it necessary to keep a patient under observation after such procedure? Has he had any patients who have been very refractory to the drug?

I have never seen any cases of pulmonary edema. How often do patients show such reactions as vomiting? I have used this type of therapy with schizophrenic patients, without any results, and the patient showed no emotional changes.

In my experience, I find that the patients tend to be euphoric after treatment and feel decidedly better.

DR. ROBERT S. BOOKHAMMER: Dr. Freed's approach to the use of chemohypnosis seems to me to be sound in that he recognizes the need to do more than merely have the patient abreact emotional experiences while under the influence of the drug. My own experience with patients who have had this treatment for a civilian neurosis has been that emotional abreaction without subsequent use of the material produced under narcosis may be even harmful. The resistance, only temporarily circumvented by barbiturates, remains as a problem the patient must deal with consciously, and it is the duty of the therapeutist to aid him in this task by going over with him in all its implications the meaning of whatever material has been produced by this method.

DR. HERBERT FREED: I want to thank the discussers for their kind and interesting remarks.

Dr. Twyeffort made a comment about the use of atropine. I have not had the unfortunate experience with pulmonary edema and perhaps I am careless. As I think of the dangers of pulmonary edema and how I treated it in insulin shock therapy, it makes me feel that I shall do more about it in the future.

Dr. Twyeffort brought out something which I tried to emphasize, that is, the hostility that comes out in these patients. One of the patients which he described had an anxiety state. Treatment brought out hostility, but she went into a state in which she required prolonged narcosis. I think that one should allow such a patient to bring out material within the limit of her anxiety tolerance by experimenting with the dosage. As to refractoriness to the drug, patients with a great deal of anxiety or alcoholic patients can be given up to 15 grains (0.975 Gm.) without securing much effect. This is especially true of alcoholic patients.

Dr. Herskovitz pointed out something with which I agree for the most part, but not completely. I do not think the action is simply a matter of lessening repression. I feel that barbiturates have a specific effect. In my experience, practically every patient given barbiturates showed euphoria at some stage. I have not given alcohol to patients as a substitute for the barbiturates. Dr. Thorner, of this society, has administered alcohol by tube. Some have even

given it intravenously and claimed that it produced the same effects as sodium amytal. My feeling is that barbiturates produce a change which is different from that produced in hypnosis.

In answer to Dr. Bell's question as to how long after such a procedure one can let the patient leave, I think that once the proper dose of sodium pentothal has been achieved the patient can walk out in ten or fifteen minutes after treatment. Until one reaches the proper dose, one may have to let him lie down for a short time after treatment.

Dr. Bookhammer stresses a point which I was trying to emphasize. The important aspect in this treatment is not the giving of a drug but the knowing what to do with the material obtained. In order to get the patient to accept this material consciously, I have felt that a procedure should be used which I have experimented with only a little but hope to do more with in the near future, that is, to make a phonograph record during the treatment and then play it back to the patient afterward. I think such records would be extremely beneficial in treatment of the patient as well as for teaching purposes.

Memorial to Dr. Henry I. Klopp. Dr. Arthur P. Noyes, Norristown, Pa.

Dr. Henry I. Klopp, long a respected member of this society, died on March 15, 1945. Dr. Klopp was born in Lebanon County, Pa., Jan. 1, 1870. He was educated in the public schools of that county and at Palatinate College, Myerstown, Pa. He graduated from Hahnemann Medical College in 1894 and from 1895 to 1912 was on the staff of the Westboro (Mass.) State Hospital. In that year he became superintendent of the newly constructed Allentown (Pa.) State Hospital, a position which he held until his retirement, July 1, 1942.

Dr. Klopp contributed his services and sound judgment to many welfare agencies. A genial and friendly person, he was much beloved by his professional associates and to a remarkable degree enjoyed the confidence and respect of the community and of its organized social and welfare agencies. Tactful but courageous in public work, he was uncompromising in what he believed to be for the interests of his patients and the hospital with which he was connected. Vigorous and methodical, Dr. Klopp impressed his personality on the hospital for the development and growth of which he was responsible. Under his guidance the Allentown State Hospital became in many respects the outstanding one in the Pennsylvania mental hospital system. His career was one of outstanding service in public psychiatric work, the results of which will long do him honor.

CHICAGO NEUROLOGICAL SOCIETY

Ralph C. Hamill, M.D., *President*, in the Chair

Annual Meeting, May 8, 1945

Presidential Address: Learning and Belief. Dr. Ralph C. Hamill.

Chronic Leptomeningeal Thickening Following Treatment of Meningitis with Sulfonamide Drugs. Dr. Percival Bailey.

This paper was published in the December 1945 issue of the *Annals of Surgery*, page 917.

Penicillin Therapy for Spina Bifida. Dr. A. Earl Walker and Dr. Herbert C. Johnson.

One of the most difficult problems for the neurosurgeon is the management of infected meningoceles and meningomyeloceles. Two infants with infected meningomyelocele were treated with intrathecal injections of penicillin, with resulting elimination of the infection and conversion of the saccular meningomyelocele into a small, completely epithelized scar.

The mortality rate for the usual conservative or operative treatment of infants with spina bifida and meningocele or meningomyelocele is high. A method of medical management which would materially decrease this mortality offers a means by which the patient may be tided over for a few years, until the neurologic defect and the danger of hydrocephalus may be evaluated more accurately. It is probable that the routine use of penicillin in cases of infected or potentially infected lesions of spina bifida, especially those which are not covered with normal skin, would permit healing of the meningeal sac with a firm scar. The administration of penicillin intrathecally in daily doses of 10,000 Oxford units in 2 to 3 cc. of isotonic solution of sodium chloride would appear to be the optimum method of therapy and to invoke little reaction.

The fact that a simple, safe method is available for the treatment of infected or potentially infected lesions of spina bifida should not lead to overindulgence in its use in those cases of meningomyelocele and myelocele associated with a serious neurologic defect. If the paralysis is obviously so severe that the patient cannot develop into a socially acceptable person, the administration of penicillin, although it may allow the spinal defect to heal, is contraindicated both on sociologic and on economic grounds. It seems unlikely that the use of penicillin in selected cases of spina bifida will introduce social problems.

DISCUSSION

DR. PAUL C. BUCY: The treatment of spina bifida is a problem which has concerned me for a number of years. I should like to stress the point made in the latter part of the paper. In dealing with cases in which there is a neurologic defect I have never regretted having withheld treatment, but on several occasions I have regretted treating these severely deformed infants. I believe it is unwise to treat any child with meningocele who has a severe incapacitating neurologic deficit with any method that has any likelihood of success. One of the greatest medical tragedies is to have such a child survive for many years with paralyzed, anesthetic legs and absence of control over the bowel and bladder.

DR. HERBERT C. JOHNSON: Dr. Walker has done considerable work on penicillin and its convulsive effect on the central nervous system. Early in the investigation the question was raised whether the convulsive factor was due to impurities or was inherent in the penicillin itself. With a number of methods, attempts were made to separate the convulsive factor from the antibiotic factor. In almost all experiments, however, it was found that when the antibiotic factor was destroyed to a certain degree the convulsive factor was proportionately diminished in potency.

A definite answer to the statement that the convulsive activity of penicillin is due to impurities can now be made, since recently we obtained an amount of pure crystalline sodium penicillin. Experiments have shown that pure penicillin is just as potent in producing convulsions as is commercial penicillin. It is apparent, then, that the convulsive activity of penicillin is not due to impurities present in the commercial product.

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following candidates were certified at a meeting of the board in Chicago, May 24 and 25, 1946.

Psychiatry.—By Examination: Samuel E. Abel, Murfreesboro, Tenn.; James A. Alston, Providence, R. I.; Florence O. Austin, Patton, Calif.; Julius Barasch, Wingdale, N. Y.; Major Frank R. Barta, M.C., A.U.S. (formerly New Haven, Conn.); Leo Henry Bartemeier, Detroit; Charles R. F. Beall, Atlanta, Ga.; Robert W. Beck, Milwaukee; Ada D. Bedinger, Providence, R. I.; Ivan C. Berlien, Detroit; H. Robert Blank, Brentwood, N. Y.; Melvin F. Blaurock, Oak Park, Ill.; Charles A. Bohnengel, Mooretown, N. Y.; Major William W. Bourke, M.C., A.U.S.; John D. Bradley, Durham, N. C.; Lieut. Col. Charles A. Brown, M.C., A.U.S.; William Brown, New York; Byron S. Cane, Washington, D. C.; Walter A. Carley, St. Paul, Minn.; R. Charman Carroll, Durham, N. C.; Jesse F. Casey, Topeka, Kan.; Major Louis A. Cibelli, M.C., A.U.S. (formerly Roanoke, Va.); Louis F. Cleary, Baltimore; Jules V. Coleman, Denver; Henry H. Crank, Topeka, Kan.; Lieut. Col. J. O. Crownwell, M.C., A.U.S. (formerly Blackfeet, Idaho); Capt. Leon S. Diamond, M.C., A.U.S. (formerly American Lake, Wash.); Clifford O. Erickson, Rochester, Minn.; Benjamin Erps, Downey, Ill.; * Harrison S. Evans, Columbus, Ohio; Capt. Edward G. Feldman, M.C., U.S.A. (formerly Columbus, Ohio); Raymond Fellman, Chicago; Robert H. Felix, Washington, D. C.; Major Lewis J. Fielding, M.C., A.U.S. (formerly Waco, Texas); William S. Fife, Royal Oak, Mich.; William A. Florio, Washington, D. C.; Capt. Irving A. Gail, M.C., A.U.S. (formerly Lexington, Ky.); Robert W. Gans, Memphis, Tenn.; Mark Gerstle Jr., New York; Merton M. Gill, Topeka, Kan.; Fritz Glaser, Cleveland; Benjamin H. Gottesfeld, Hartford, Conn.; Charles C. Graves Jr., Marlboro, N. J.; Burton P. Grimes, St. Peter, Minn.; Robert Gronner, Chicago; Walter M. Gysin, Omaha; William L. Harris, Kings Park, N. Y.; Paul Haun, Washington, D. C.; James R. Hawkins, Cincinnati; Capt. J. Lester Henderson, M.C., A.U.S. (formerly Pasadena, Calif.); Charles K. Hepburn, Indianapolis; Thomas V. Hoagland, Ypsilanti, Mich.; Capt. Morris Isenberg, M.C., A.U.S. (formerly Cheyenne Agency, S. D.); Valeria R. Juracsek, Ann Arbor, Mich.; Benjamin H. Kagwa, Chicago; Paul Kells, Miami, Fla.; Capt. Albert Kraus, M.C., A.U.S. (formerly Chillicothe, Ohio); Othilda Krug-Brady, Cincinnati; Edward E. Landis, Louisville, Ky.; Charles E. Leonard, Oklahoma City; Harold N. Levine, Woodside, N. Y.; Anne G. Levingston, Waltham, Mass.; David Levitin, Chicago; Theodore Lidz, Baltimore; James V. Lowry, Lexington, Ky.; Lieut. Col. Henry Luidens, M.C., A.U.S. (formerly Cleveland); Major Norman C. Mace, M.C., A.U.S. (formerly American Lake, Wash.); Capt. Aaron W. Mallin, M.C., A.U.S. (formerly Northport, N. Y.); Ben Marks, Detroit; Major Aaron S. Mason, M.C., A.U.S. (formerly Downey, Ill.); Robert L. Meller, Minneapolis; Brig. Gen. William C. Menninger, M.C., A.U.S. (formerly Topeka, Kan.); *Lieut. Herman A. Meyersburg, (MC) U.S.N. (formerly Charlottesville, Va.); Donald F. Moore, Ypsilanti, Mich.; Donald P. Morris, Dallas, Texas;

* The asterisk denotes complementary certification.

Raymond J. Norfray, Chicago; Jacob P. Norman, Foxboro, Mass.; Douglas W. Orr, Seattle; Col. Ernest H. Parsons, M.C., A.U.S. (formerly Washington, D. C.); Samuel Paster, Memphis, Tenn.; Stanley Peal, Towson, Md.; Frank P. Pignataro, Marlboro, N. J.; William W. Pike, Orangeburg, N. Y.; Major Simon Polan, M.C., A.U.S. (formerly Philadelphia); Isidore Portnoy, New York; Edward S. Post, Marion, Ind.; Jack Rapoport, New York; James E. Rappa, Brooklyn; Donald R. Reader, Fort Snelling, Minn.; Major Lewis L. Robbins, M.C., A.U.S. (formerly Topeka, Kan.); Isadore Rodis, Washington, D. C.; Capt. Samuel R. Rosen, M.C., A.U.S. (formerly Brooklyn); Ernst Schmidhofer, Chicago; Laurence A. Senseman, Saylesville, R. I.; Melvin Simonson, Downey, Ill.; Lieut. Col. Beverley E. Smith, M.C., A.U.S. (formerly Washington, D. C.); Capt. Manuel Straker (formerly London, Ontario, Canada); Joseph D. Sullivan, New York; Major George F. Sutherland, M.C., A.U.S. (formerly Belmont, Mass.); Virginia S. Tarlow, Chicago; Lieut. Col. Joseph C. Tatum, M.C., A.U.S. (formerly Washington, D. C.); Oreon K. Timm, Fort Custer, Mich.; John D. Trawick Jr., Bethesda, Md.; Chester Wade, Oconomowoc, Wis.; Julius M. Wallner, Ann Arbor, Mich.; Joseph Walzer, New York; William Weisdorf, Chicago; C. A. Whitaker, Oak Ridge, Tenn.

Neurology.—By Examination: John L. Garvey, Milwaukee; Heinz Kohut, Chicago; Vasilios S. Lambros, Washington, D. C.; William H. Sweet, Boston; Joseph Zimmerman, Brooklyn.

Psychiatry and Neurology.—By Examination: Daniel W. Badal, Cleveland; Joe R. Brown, Minneapolis; Rawley E. Chambers, Denver; Major Walter L. Ford, M.C., A.U.S. (formerly St. Louis); Bernard R. Goldberg, Newark, N. J.; Robert H. Groh, Washington, D. C.; Capt. Avraam T. Kazan, M.C., A.U.S. (formerly New York); Henry D. Lederer, Cleveland; Louis Linn, New York; Robert J. Mueller, St. Louis; Julius L. Rosenbloom, Pueblo, Colo.; Isadore Spark, Philadelphia; Walker Thompson, New Orleans; Henry D. Von Witzleben, Chicago; Cornelia B. Wilbur, New York; Joseph M. Zucker, Providence, R. I.

Psychiatry.—On Record: William M. Bevis, St. Petersburg, Fla.; Clarence G. Cox, Milledgeville, Ga.; William M. Dobson, Northampton, Mass.; C. L. Fessenden, Kings Park, N. Y.; E. Moore Fisher, Washington, D. C.; John A. Holland, Cleveland; James P. Kelleher, Rome, N. Y.; Marion R. King, Washington, D. C.; Edwin M. Levy, Canandaigua, N. Y.; Mary MacLachlan, Kings Park, N. Y.; Clarence R. Miller, Coatesville, Pa.; Major Henry S. Mitchell, M.C., A.U.S. (formerly Baltimore); Erwin H. Mudge, Helmuth, N. Y.; Appleton H. Pierce, Philadelphia; Philip J. Trentzsch, New York; John L. Van de Mark, Rochester, N. Y.

Psychiatry and Neurology.—On Record: Winthrop Adams, Boston; Aclpfar A. Marsteller, Washington, D. C.; Leonard Ravitz, Cleveland; Julius Sobin, Newark, N. J.

REFRESHER COURSE IN PSYCHIATRY, UNIVERSITY OF CALIFORNIA

The University Extension, University of California, in cooperation with the Division of Psychiatry, University of California Medical School, announces a twelve weeks' refresher course in psychiatry and neurology, starting Monday, Sept. 16, 1946, at the Langley Porter Clinic, University of California Medical School.

This course is a repetition of the course in psychiatry and neurology offered in January, February and March 1945, with minor changes. It is open to physicians generally, particularly to those returning from the armed forces. Registration is tentatively limited to sixty physicians, and the University of California reserves the right to give preference to its own graduates and to veteran physicians.

Instruction will be given under the direction of Dr. K. M. Bowman, professor of psychiatry, University of California Medical School, with the assistance of staff members from the various divisions of the medical school.

Registration is open to graduates of approved medical schools with nine months' general internship. Immediate application for registration is recommended. It should contain the following information: (1) place of legal residence, (2) medical school attended and date of graduation, (3) experience and training in psychiatry and (4) short record of military service. Applications should be addressed to: Stacy R. Mettier, M.D., head of postgraduate instruction, Medical Center, University of California, San Francisco 22.

The fee for the course will be $200, payable in advance. Candidates registered under the provisions of the G. I. Bill of Rights will receive a refund, prorated according to their terminal leave. Enrolment fee should be either enclosed in letter or mailed immediately, with check or money order payable to the Regents of the University of California (for "Course in Psychiatry").

Further details regarding this course may be obtained from the Langley Porter Clinic, Overland 8080, or from the office of Dr. Mettier, Montrose 3600, Local 255 (secretary).

FELLOWSHIPS FOR TRAINING IN CHILD GUIDANCE CLINIC PSYCHIATRY

The National Committee for Mental Hygiene, Inc., offers fellowships for training in child guidance clinic psychiatry. The training is for positions in community clinics where psychiatrists, psychologists, social workers and others collaborate in the treatment of children suffering from emotional or mental illness.

Some of the fellowships are for two years; some for one year. The stipend is from $2,600 to $3,000 for the first year and more for the second year. Prerequisites are graduation from an approved medical school, a general internship and two years of general psychiatry. Military psychiatry will be accepted for at least a part of the two years.

Opportunity is provided for the fellow to develop his own skills in a well organized service, with the support of a carefully planned training program and adequate supervision. The training centers are selected on the basis of standards which have been established by the National Association of Child Guidance Clinics.

For further information write to Dr. Milton E. Kirkpatrick, Director, Division on Community Clinics, the National Committee for Mental Hygiene, Inc., 1790 Broadway, New York 19.

Obituaries

WALTER EDWARD DANDY, M.D.
1886-1945

Walter Dandy is dead. To those who knew his abundant vitality and driving energy, and his forcefulness, even in recent days, in presenting his views and convictions, Dandy has been so vital a person that it is difficult to believe that his voice will no longer be heard. He died as a result of coronary thrombosis, suddenly, on April 19, 1946. He leaves a son, Walter, who is in medical school; three daughters, Mary, Kathleen and Margaret, and his wife, Sadie Martin, whom he married in 1924.

Born in Sedalia, Mo., April 6, 1886, of parents from England and North Ireland, Walter Edward Dandy attended the public schools of Sedalia and the University of Missouri and entered the Johns Hopkins University School of Medicine in 1907, with advanced standing. He graduated with the degree of Doctor of Medicine in 1910 and continued his work in this medical school and hospital, rising through the various stages of the surgical service and academic rank, to become adjunct professor of neurological surgery in 1932.

Within three years after receiving the M.D. degree he had, with characteristic energy and industry, completed and published three scientific studies, one on the youngest human embryo which had been studied up to that time, one on the blood supply of the pituitary body and one on the nerve supply of this intracranial structure. His classic work, "An Experimental and Clinical Study of Internal Hydrocephalus" (*J. A. M. A.* **6**:2216 [Dec. 20] 1913), was published in 1913, when he was 27 years old. Five years later he produced another classic, on pneumoventriculography (*Ann. Surg.* **68**:5-11, 1918), a procedure which he originated and which has been very valuable in the precise localization of intracranial lesions. It has repeatedly been said that ventriculography has been the greatest single contribution to brain surgery ever made.

Dandy's mastery of neurosurgical technic enabled him to make a brilliant series of technical contributions, impressive even in the form of a partial list: operations for the complete removal of acoustic neurinomas, radical new operations for trigeminal neuralgias and neuralgias of other cranial nerves, and operations for torticollis and

for Ménière's disease. His characteristic combination of care in procedure and boldness of aim was well exhibited in his operations for the removal of congenital aneurysms of the arteries forming the circle of Willis and of their large branches. Again, his self-confident independence of judgment and his virtuosity in surgical technic were demonstrated in his operations for ruptured intervertebral disks, a condition which he discovered and reported in 1929.

Much of Dandy's success in making discoveries and innovations was made possible by his courage and independence of judgment, but boldness was by no means the only, or principal, virtue of his work. His improvement in the surgical treatment of cerebral abscess by utilizing aspirations through tiny trephine openings in the skull was an example of the value he placed on conservative technic.

Dr. Dandy was a member of the American Surgical Association, the American Neurological Association, the Southern Medical Association, the Southern Surgical Association, the American Medical Association, Phi Beta Kappa and Sigma Xi.

In addition to his scientific reports in journals, portions of Dandy's large experience were published in a series of books, among which are "Benign Tumors of the Third Ventricle, Their Diagnosis and Treatment," Springfield, Ill., Charles C Thomas, Publisher, 1933; "Benign, Encapsulated Tumors in the Lateral Ventricles of the Brain; Diagnosis and Treatment," Baltimore, Williams and Wilkins Company, 1934; "Orbital Tumors," New York, Oskar Piest, 1941; "Intracranial Arterial Aneurysms," Ithaca, N. Y., Comstock Publishing Co, Inc., 1944.

Besides his direct contributions to neurosurgery, Dandy has inspired by his example a series of brilliant younger neurosurgeons, who worked with him and through whose work he will continue to be a living force for further advancement.

The outstanding clarity and succinctness of Dandy's paper were the expression of a forthright habit of mind, which sometimes also involved him in stormy controversies and a few personal enmities; but he regularly emerged from such disputes with the increased respect of his scientific colleagues, and it can be safely predicted that his stature as a great figure in medicine will grow in the perspective of time. His international reputation brought him large numbers of patients, and he did a tremendous amount of work. Simple and unpretentious in manner, generous in many unpublicized ways and simple in his personal tastes, he was a delightful friend and companion. There is much personal sorrow at his death, as well as regret at the cessation of a brilliant career of investigation and service for the relief of human suffering.

JOHN C. WHITEHORN, M.D.

LADISLAV HAŠKOVEC, M.D.
1866-1944

Ladislav Haškovec, professor ordinarius of neurology and psychiatry in Prague since 1919, died during the German occupation of Czechoslovakia, on Jan. 16, 1944.

Ladislav Haškovec was the founder of Czechoslovakian neurology, which he separated from and made independent of internal medicine. He was a pupil of the famous French neurologists Charcot and Gley, and his publications and papers showed the ingeniousness and brilliancy of the French school of neurology. He wrote more than two hundred scientific publications in various fields of neurology, neurohistopathology, psychiatry, endocrinology, eugenics and mental hygiene. The most outstanding and fundamental publications were devoted to akathisia, pilomotor reflex, histopathologic observations in cases of paralysis agitans, localization of the center for consciousness, activity of the thyroid and parathyroid gland, infantile speech in adults, traumatic and vegetative neuroses, contractures and tremor.

For over thirty years he published and edited the Czechoslovakian journal *Revue v neuropsychopathologi*. He was a member of numerous medical societies and institutions all over the world. In 1930 he was nominated chairman of the First International Congress of Mental Hygiene, in New York, and in 1935, vice president of the Second International Congress of Neurologists, in London.

Ladislav Haškovec will be remembered by his friends and pupils as a noble and generous man, and his death is a loss to his country as well as to neurology, which he enriched by many original and interesting contributions.

JOSEPH A. WINN, M.D.

CORRECTION

In the article by Dr. Robert Wartenberg entitled "Associated Movements in the Oculomotor and Facial Muscles," in the May issue (ARCH. NEUROL. & PSYCHIAT. **55:** 439, 1946), it is stated: ". . . the gastrolacrimal reflex, and the auriculotemporal syndrome . . . are not uncommon but, oddly enough, are not even mentioned in such a detailed work as Wilson's [1] Neurology." This is not correct. Wilson, on page 379 (Neurology, London, Edward Arnold & Co., 1940), under "trigeminal nerve," does mention the auriculotemporal syndrome. Concerning the gustolacrimal reflex he says, under facial nerve (page 403): "Lachrymation develops at times during facial overaction, e. g., in the process of eating."

Book Reviews

What People Are. By Clark W. Heath, M.D., in collaboration with others. Price, $2. Pp. 137. Cambridge, Mass.: Harvard University Press, 1945.

To describe, rather than to define, a normal young man, two psychiatrists, an internist, a physiologist, a physical anthropologist, a psychologist and a personnel worker, under the auspices of the Grant Foundation, have been accumulating data for the past six years. The initial report of their study is presented by one of them, Clark W. Heath, in this small, lucid volume.

The Grant Study is an institution which was established in 1938 at Harvard University for the study of normal persons; its aims are to find, relate and explain the characteristics of healthy young men and to seek methods and gain wisdom which will direct people to suitable training and careers and help them live happier, more successful lives.

An arbitrary concept of normal as "balanced" is first stated, then automatically defined by the method of selection of the young men. For this work, college sophomores were selected as the best available group, and only those were studied who were doing satisfactory work and whose "adjustment" was at least average. In a series of personal interviews, the frequency and technic of which are described, the investigators mentioned use eight different disciplines or methods of study: measurement of soundness, outstanding personality traits, adjustment (environmental and intrapersonal) and socioeconomic, morphologic, physiologic, medical and mental status. An interesting descriptive analysis of these disciplines makes up the bulk of this report. Integration of observations with the different disciplines is also presented.

The material is interesting for itself, but more noteworthy are the constant reminders, both stated and implied, that the work is just a tiny beginning, an infinitesimal portion of a field for observation which is vast, complex and substantially unexplored.

Questions must inevitably arise in the mind of any reader as to the criteria for selection of subjects for study or the objectivity of the interviewers. One may object to the tendency to imply desirability or goodness to certain of the character traits, always from the standpoint of career guidance and social adaptation. Or one may object to the use of terms such as "sound," "healthy" or "well integrated." But the modesty with which the author states the scope of the report indicates simply that further and enlarged studies are needed, not that this small beginning is a poor one.

Many more people from all walks of life must be investigated by representatives of more and varied disciplines before conclusions can be formulated, common denominators found or a decision made as to whether the study of normal persons can be sufficiently resolved as to be worth while. This volume offers each reader a point of departure for ideas for further study according to his own special interest.

Klinische und erbbiologische Untersuchungen über die Heredoataxien. By T. Sjögren. Acta psychiatrica et neurologica, supplement 27. Price, 15 kroner. Pp. 200, with 25 tables. Copenhagen: Einar Munksgaard, 1943.

Sjögren has long been known to students of heredity in relation to neurologic disorders, having had abundant opportunities for genetic investigations in the relatively stationary population of Sweden. His industry in the assembling of data in the present large investigation is noteworthy, and his mathematical handling of the material is commendable, if somewhat beyond the scope of the average neu-

rologist. This volume comprises a study of 188 cases of the heredoataxias, occurring in 118 families, and investigations covering a total of 3,111 persons. Cases occurring in family groups are reported, and maps are appended to show the geographic relationships. The present observations are not so striking as were those in the author's previous studies on Huntington's chorea, in which parish records indicated the inheritance of the disease through as many as nine generations. In the present investigation the disease was traceable through five generations. From his study, in which records were available over several decades, the author concludes that definite mental deterioration takes place in the end stages of both Friedreich's disease (hereditary spinal sclerosis) and Marie's heredoataxia (hereditary cerebellar ataxia) and, furthermore, that muscular atrophy occurs late in the disease in many cases. The average age of onset of Friedreich's ataxia is 13 $\pm$ 0.7 years, while that for Marie's ataxia is 34 $\pm$ 1.9 years and that for a heterogeneous group is 50 $\pm$ 2.3 years. The age at which the disease develops is determined by the family, the similarity of age being especially noticeable in siblings. The author's fourth type of the disease, *forme fruste,* shows little tendency to progression and is not accompanied with dementia or muscular atrophy, although there may be a positive Babinski sign, loss of reflexes and the telltale Friedreich's foot.

Genetic analysis shows that Friedreich's ataxia is a recessive monohybrid, whereas Marie's ataxia is overwhelmingly a dominant monohybrid; from the genetic standpoint, therefore, these two diseases are different. The heterozygotes seem to occur in small groups in various parts of the country. The material was too small for investigation of twins.

Sjögren's study is a solid contribution to genetics as related to neurologic disorders; it is well documented and beautifully printed.

The Psychiatric Novels of Oliver Wendell Holmes. Abridgment, Introduction and Annotations. By Clarence P. Oberndorf. Price, $3. Pp. 268. New York: Columbia University Press, 1943.

Oberndorf has undertaken to dissect, condense and explain the three novels of Holmes that deal especially with psychologic problems, namely, "Elsie Venner," "The Guardian Angel" and "A Mortal Antipathy." Each of these novels presents a hero or a heroine whose adjustment has been warped by circumstances, and, while a "cure" is forthcoming in the last two, Elsie Venner went to her death in what might be considered a catatonic episode. The "cures" savor somewhat of shock, since an overturned boat in Myrtle Hazard's case and a fire in the home of Maurice Kirkwood, with the attendant circumstances, resulted in progressive readaptation. Holmes's novels are old-fashioned, with their dialogue, their dissertations by various characters and the rather cumbersome working out of the plots. There is, however, a certain felicity of expression that Oberndorf has retained, so that the essentials of each story stand out in strong relief. "Many of the pasages which my pencil underscored," he writes, "were so anticipatory and far-sighted, so cogent and valid in psychiatric thought today that I could not refrain from making comments upon them here and there."

This procedure has resulted in a series of notes which detract from the stories. The annotations are superficial, anecdotal and patronizing. After all, Holmes was not the immediate precursor of Freud, nor did he live in a world of barrenness as far as psychologic motivation was concernd. The Boston of Holmes's era was alive with querying in the psychologic sphere, and, while the conservative element among Holmes's professional brethren may not have been acutely aware of the theories propounded, P. P. Quimby and Mary Baker Eddy remain as landmarks in psychotherapeutic thought. Oberndorf regards Holmes as a gifted amateur, apparently, and damns with faint praise when he compares him with the master, Freud.

Mental Changes After Excision of Cerebral Tissue: A Clinical Study of 16 Cases of Resections in the Parietal, Temporal and Occipital Lobes. By G. Rylander. Acta psychiatrica et neurologica, supplement 25. Price, 12 kroner. Pp. 81. Copenhagen, Einar Munksgaard, 1943.

This is a companion piece to the study, published in 1939, dealing with mental changes after resection of the frontal lobes in 32 cases of tumor. In the present study, Rylander has employed the same methods of examination, controlling each observation by similar studies on a member of the family or a close associate and then applying statistical methods to determine the differences. Each patient was given a standard intelligence test, and various other tests which had revealed characteristic differences in the frontal lobe series were used. Rylander points out that none of his patients showed significant losses in intellectual performance as long as the centers of the intellectual machinery (speech, gnosia) were essentially undamaged. Furthermore, none of his patients showed euphoria, restlessness or silliness, and most of them were reported to be of the same temperament after operation as before development of the symptoms of tumor. Most of the patients exhibited some falling off in endurance, some loss of memory and slight irritability, and these alterations can probably be explained by the general reduction in brain mass. Difficulties met with because of impaired vision and epileptic seizures, however, caused a gloomy personal outlook in some cases.

The author points out that extensive resections may be undertaken in the parietal, temporal and occipital lobes without damaging the capacity of the patient as long as the language centers are uninvolved. This statement contrasts strongly, however, with his observations on resection of the frontal lobes, a procedure which involves "the risk of mental invalidism in patients doing mental or other complicated work."

Rylander has given an excellent picture of the integrity of the personality when the posterior portions of the brain are attacked, and he thereby points out the specific qualities in the personality that are impaired after resection of the frontal lobe. In view of the increasing interest in the subject of psychosurgery, these monographs by one of Sweden's foremost investigators should be studied with care. The author points to the necessity of carefully controlled observations, with preoperative and postoperative tests by the same investigator, who should also be present at the operation in order to ascertain the exact portion of the brain removed. "The method is laborious, but it should yield results with a sound background of reality."